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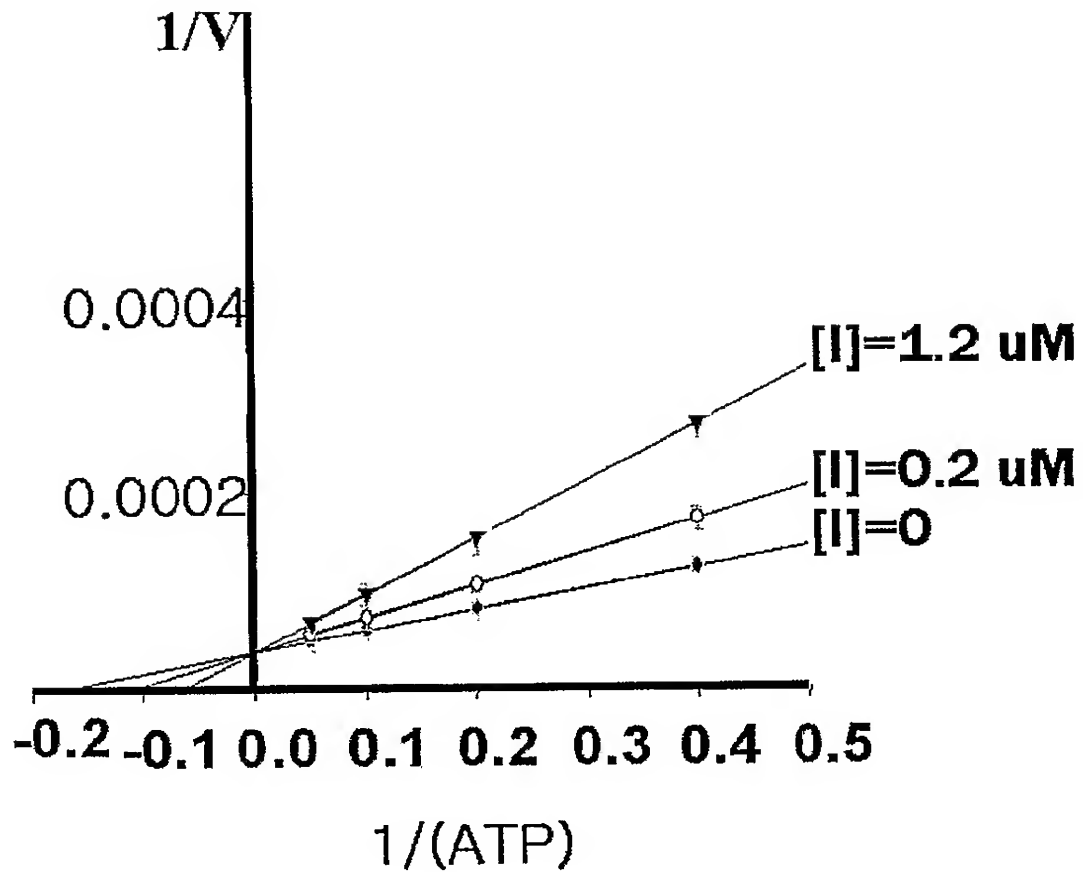
(54) Title: COMPOUND FOR INHIBITING TYROSINE KINASE ACTIVITY OF DDR2 PROTEIN



(57) Abstract: A new furopyrimidine compound, their pharmaceutically acceptable salt, and a tyrosine kinase activity inhibitor. The furopyrimidine compound is a compound defined by chemical formula 1, 2, 3 or 4, on their precursor, and can exist as a form of free base or in an acid-addition salt. Since the furopyrimidine compound has an effect of inhibiting activity of DDR2 tyrosine kinase, it can be used in treating illnesses caused by the DDR2 tyrosine kinase activity such as hepatocirrhosis, rheumatoid arthritis or cancer.

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COMPOUND FOR INHIBITING TYROSINE KINASE ACTIVITY OF DDR2 PROTEIN

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a new furopyrimidine compound, their phamaceutically acceptable salt, and a tyrosine kinase activity inhibitor. Since the furopyrimidine compound of the present invention suppresses activity of DDR2 (Discoidin Domain Receptor 2) tyrosine kinase, it can be used for treatment of illnesses on which the DDR2 tyrosine kinase activity works such as liver cirrhosis, rheumatoid arthritis, cancer, or the like.

2. Description of the Background Art

The Discoidin Domain Receptor (DDR) belongs to a protein family of a receptor tyrosine kinase using collagen as an activity ligand and there are two types of DDR protein, DDR1 and DDR2. These proteins include an outer cell portion (N-end), a transmembrane portion and a cytoplasm portion (C-end), and has a portion indicating a tyrosine kinase activity at the C-end portion, which is exposed to cytoplasm.

The DDR protein has been revealed to work to enhance development of fibroblast, hepatic stellate cell of liver tissue, a synovial fibroblast extracted from a patient with rheumatism, collagen synthesis by these cells, and generation of MMP-1 or MMP-2. In such cases, the tyrosine kinase activity of the DDR2

protein is known to be critical. In addition, it has been reported that there is an increase of expression of the DDR2 protein in metastatic cancer cells. These facts indicate that type tyrosine kinase activity of the DDR2 protein can be a new target of development of new treatments for fibrosis lesion of the tissue, rheumatism or cancer.

Presently, development of a new low-molecule medicine is largely focused on the development of a compound for interfering with the attachment of an ATP to an active pocket by targeting an enzyme activation pocket of a target kinase, and its typical example is a recently-developed medicine called EGFR, a new kinase-inhibiting medicine called Iressa and an abl kinase inhibitor called Glivec.

SUMMARY OF THE INVENTION

Therefore, an object of the present invention is to furovide a new low-molecule compound for inhibiting DDR2 tyrosine kinase activity and a medical treatment caused by tyrosine kinase activity of DDR2 protein including the same, in order to treat a disease caused by tyrosine kinase activity of DDR2 protein represented by a tissue fibrosis, rheumatism and cancer.

The inventors of the present invention has invented a new low-molecule compound inhibiting activity by inhibiting ATP bonding to the active pocket of DDR2 tyrosine kinase, which can inhibit major morbid phenomenon appearing in diseases such as liver cirrhosis, rheumatism or cancer, and as such the inventors have completed the present invention by confirming that the new low-molecule compound can be utilized as an excellent treatment to those diseases.

To achieve these and other advantages and in accordance with the purpose of the present invention, as embodied and broadly described herein, a new furopyrimidine compound which inhibits tyrosine kinase activity of DDR2 protein, its precursor, their pharmaceutically acceptable salt and treatment of diseases related to tyrosine kinase activity of the DDR2 protein containing the same is furovided.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are included to furovide a further understanding of the invention and are incorporated in and constitute a part of this specification, illustrate Examples of the invention and, together with the description, serve to explain the principles of the invention.

In the drawings:

Figure 1 is a graph showing that a compound in accordance with the present invention inhibiting DDR2 kinase activity by an ATP competitive mechanism, and specifically, showing a result of a reaction rate which was obtained by changing an amount of ATP, the substrate, at various densities of the compound which was then reciprocally plotted;

Figure 2 is an electrophoresis photo showing an inhibiting activity of the compound of the present invention with respect to tyrosine phosphorylation of DDR2 protein induced by a first type collagen in hepatic stellate cell HSC T6;

Figure 3 is a graph showing viability of treated cell with the density of the chemical treatment;

Figure 4A is a graph showing that the compound in accordance with the

present invention is treated in an HSC T6 cell cultivation solution and an amount of relative MMP-2 of the cultivation solution was quantitatively measured through ELISA using an MMP-2 specific antibody;

Figure 4B shows that after HSC 6 cell was treated with the compound in accordance with the present invention, the amount of smooth muscle actin in the cell was quantitatively measured by using western blotting which utilizes a smooth muscle specific antibody;

Figure 5 is an electrophoresis photo showing a degree of apoptosis according to DNA fragmentation of the compound-treated HSC T6 cell according to each processing density of the compound;

Figure 6 is a photo showing a liver tissue obtained by injecting the compound dissolved in a carrier or in a DMSO in accordance with the present invention by 10mg/kg to a tail vein of a mouse, which underwent a bile duct suture, for two weeks and a liver tissue obtained from a mouse that was left after having underwent a simulation operation (placebo) through a control experiment was frozen, a frozen thin film was created and dyed through a detrition dying method, and then, observed through a 400 magnification microscope;

Figure 7 is a graph showing a viability of a synovial fibroblast extracted from a rheumatism patient to which the compound in accordance with the present invention was treated through the density of the compound;

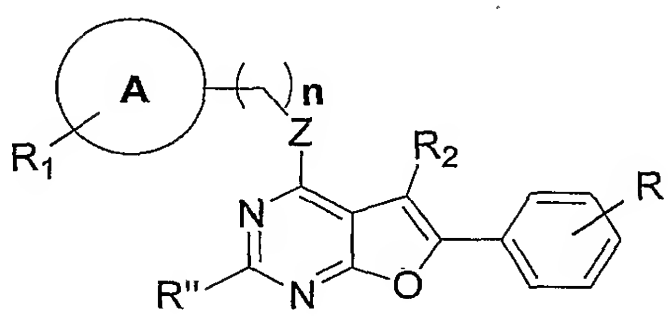
Figure 8 is an electrophoresis photo showing comparison of an amount of MMP-1 mRNA of the synovial fibroblast when the compound in accordance with the present invention was treated and when the compound in accordance with the present invention was not treated.

DETAILED DESCRIPTION OF THE PREFERRED EXAMPLES

The furopyrimidine compound of the present invention has the effect of inhibiting activity of the DDR2 tyrosine kinase, so it can be used for treating illnesses related to the DDR2 tyrosine kinase activity.

the present invention furovides a furopyrimidine compound, which inhibits tyrosine kinase activity of DDR2 protein and is defined by Chemical Formula (1) incorporated with various derivatives in a furopyrimidine ring, its precursor and its pharmaceutically acceptable salt:

[Chemical Formula 1]



wherein, Z is O, S or NH,

n represents an integer between 0 and 4,

R_1 may be single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, amidine, C1-C4 alkyl group, C1-C4 halo alkyl group, C1-C7 alkoxy group, C1-C4 alkyl amino group, C1-C4 alkylthio group, C1-C4 alkyl amide group, C1-C4 acyl amino group, C1-C4 acyl oxy group, C1-C4 alkyl sulfone amide group, C1-C4 alkyl sulfonate group, imidic acid C1-C4 alkyl ester, thioimidic acid C1-C4 alkyl ester, hydroxy or amino, morpholine, acetate, acetamide, methanesulfoneamide group-substituted methyl group, C1-C4 halo alkyl group, C1-C4 alkoxy group, or a halogen-substituted benzyl oxy group,

R" represents hydrogen, C1-C4 alkyl group, C1-C4 halo alkyl group, C1-C7 alkoxy group, C1-C4 alkyl amino group, C1-C4 alkyl thio group, C1-C4 alkyl amide group, C1-C4 acyl amino group, C1-C4 acyl oxy group, imidic acid C1-C4 alkyl ester, thiol-imidic acid C1-C4 alkyl ester, hydroxy or amino, morpholine, acetate, acetamide, methanesulfoneamide group-substituted methyl group, C1-C4 halo alkyl group, C1-C4 alkoxy group, or a halogen-substituted phenyl group,

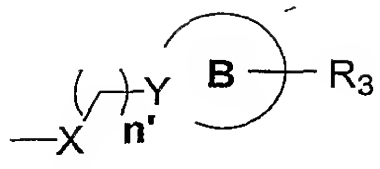
A ring indicates benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyrazine, pyridazine, pyrimidine, cyclo hexyl, piperidine or morpholine,

R_2 indicates hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C5 alkyl group, C1-C5 haloalkyl group, alkylester, phenyl group, halogen-substituted phenyl group, C1-C4 alkoxy group-substituted phenyl group or C1-C4 haloalkoxy group-substituted phenyl group, and

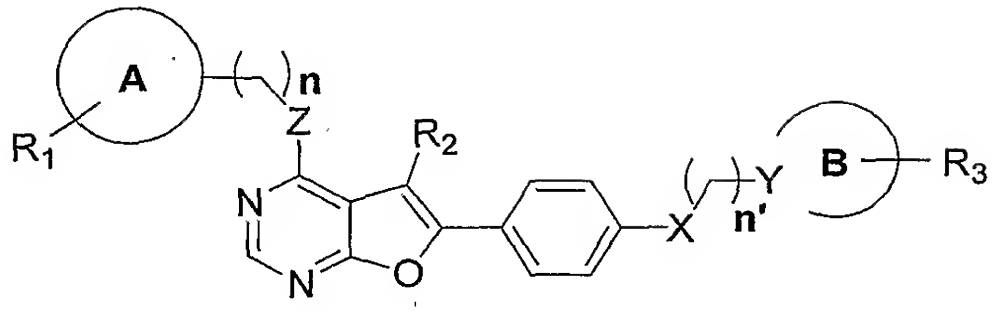
R may be single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, amidine, C1-C4 alkyl group, C1-C4 haloalkyl group, C1-C7 alkoxy group, C1-C4 alkylamino group, C1-C4 alkylthio group, C1-C4 alkylamide group, C1-C4 acylamino group, C1-C4 acyloxy group, or C1-C4 alkylsufoneamide group.

In addition, in the present invention, the substituent R of the Chemical Formula 1 is a compound of Chemical Formula 5 for inhibiting tyrosine kinase activity of DDR2 protein, and R" is a furopyrimidine compound defined by the following Chemical Formula 2, hydrogen, its precursor, and its pharmaceutically acceptable salt:

[Chemical Formula 5]



[Chemical Formula 2]



wherein, Z is O, S or NH,

X is O, S or NH,

Y is C or N, n is an integer between 0 and 4,

n' is an integer between 0 and 4,

R_1 and R_3 are independently identical or different and may be single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, amidine, C1-C4 alkyl group, C1-C4 halo alkyl group, C1-C7 alkoxy group, C1-C4 alkyl amino group, C1-C4 alkylthio group, C1-C4 alkyl amide group, C1-C4 acyl amino group, C1-C4 acyl oxy group, C1-C4 alkyl sulfoneamide group, C1-C4 alkyl sulfonate group, imidic acid C1-C4 alkyl ester, thioimidic acid C1-C4 alkyl ester, hydroxy or amino, morpholine, acetate, acetamide, methanesulfoneamide group-substituted methyl group, C1-C4 halo alkyl group, C1-C4 alkoxy group, or a halogen-substituted benzyl oxy group,

A ring indicates benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, cyclo hexyl, piperidine or morpholine,

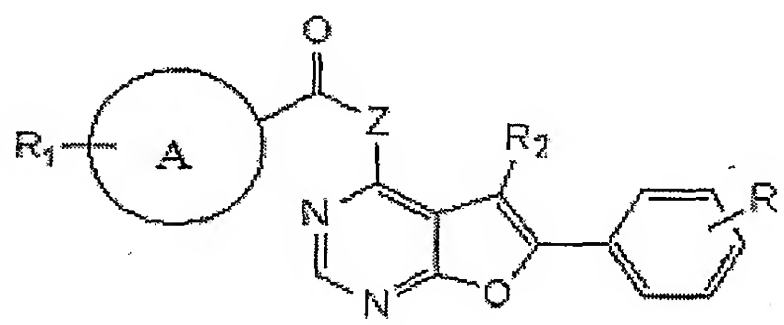
B ring indicates pyrrole, imidazole, oxazole, thiazole, triazole, pyrazole,

pyridine, pyrazine, pyridazine, pyrimidine, piperidine, pyrolidine, piperazine, morpholine, thiomorpholine, imidazoline, pyrolidon, C3-C6 cycloalkyl or piperidon, and

R_2 indicates hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C5 alkyl group, C1-C5 haloalkyl group, alkylester, phenyl group, halogen-substituted phenyl group, C1-C4 alkoxy group-substituted phenyl group or C1-C4 haloalkoxy group-substituted phenyl group.

In addition, the present invention furovides a furopyrimidine compound defined by the following Chemical Formula 3 for inhibiting tyrosine kinase activity of DDR2 protein, its precursor, and its pharmaceutically acceptable salt:

[Chemical Formula 3]



wherein, Z is O, S or NH,

n is an integer between 0 and 4,

R_1 may be single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, amidine, C1-C4 alkyl group, C1-C4 halo alkyl group, C1-C7 alkoxy group, C1-C4 alkyl amino group, C1-C4 alkylthio group, C1-C4 alkyl amide group, C1-C4 acyl amino group, C1-C4 acyl oxy group, C1-C4 alkyl sulfone amide group, C1-C4 alkyl sulfonate group, imidic acid C1-C4 alkyl ester, thioimidic acid C1-C4 alkyl ester, hydroxy or amino, morpholine, acetate, acetamide, methanesulfoneamide group-substituted methyl group, C1-C4 halo alkyl group, C1-C4 alkoxy group, or a

halogen-substituted benzyl oxy group,

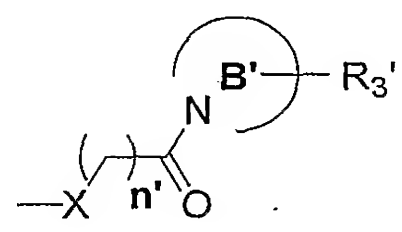
A ring indicates benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, cyclo hexyl, piperidine or morpholine,

R_2 indicates hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C5 alkyl group, C1-C5 haloalkyl group, alkylester, phenyl group, halogen-substituted phenyl group, alkoxy group-substituted phenyl group, or C1-C4 haloalkoxy group-substituted phenyl group, and

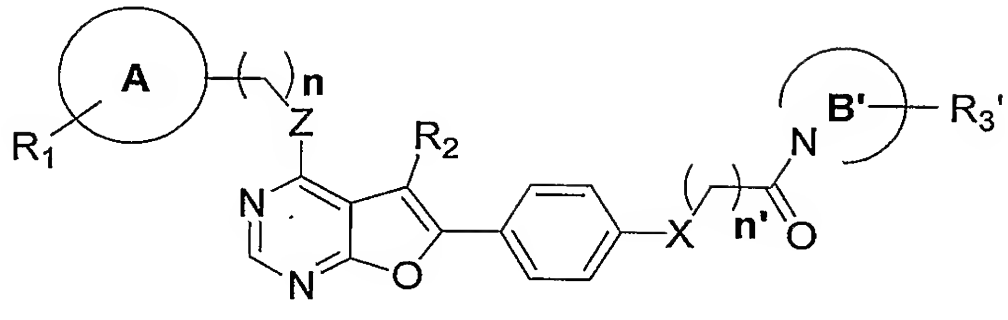
R may be single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C4 alkyl group, amidine, C1-C4 haloalkyl group, C1-C7 alkoxy group, C1-C4 alkylamino group, C1-C4 alkyl thio group, C1-C4 alkyl amide group, C1-C4 acylamino group, C1-C4 acyloxy group, or C1-C4 alkylsufoneamide group.

In addition, in the present invention, the substituent R of Chemical Formula 1 is a compound of Chemical Formula 6 for inhibiting tyrosine kinase activity of DDR2 protein, and R" is a furopyrimidine compound represented by the following Chemical Formula 4, hydrogen, and its precursor, and its pharmaceutically acceptable salt:

[Chemical Formula 6]



[Chemical Formula 4]



wherein, Z is O, S or NH,

X indicates O, S or NH,

n is an integer between 0 and 4,

n' is an integer between 0 and 4,

R_1 and R_3' are independently identical or different, and may be single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, amidine, C1-C4 alkyl group, C1-C4 halo alkyl group, C1-C7 alkoxy group, C1-C4 alkyl amino group, C1-C4 alkylthio group, C1-C4 alkyl amide group, C1-C4 acyl amino group, C1-C4 acyl oxy group, C1-C4 alkyl sulfoneamide group, C1-C4 alkyl sulfonate group, imidic acid C1-C4 alkyl ester, thioimidic acid C1-C4 alkyl ester, hydroxy or amino, morpholine, acetate, acetamide, methanesulfoneamide group-substituted methyl group, C1-C4 halo alkyl group, C1-C4 alkoxy group, or a halogen-substituted benzyl oxy group,

A ring indicates benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, cyclo hexyl, piperidine or morpholine,

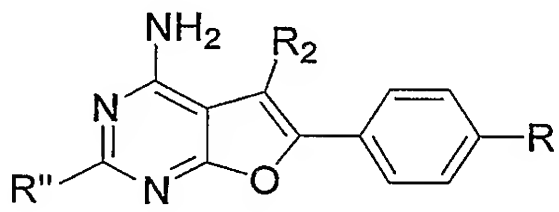
B' ring indicates pyrrole, pyrazine, pyridazine, pyrimidine, piperidine, pyrolidine, piperazine, morpholine, thiomorpholine, imidazoline, pyrolidon or piperidon, and

R_2 indicates hydrogen, halogen, cyano, nitro, hydroxyl, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C5 alkyl group, C1-C5 haloalkyl group, alkylester, phenyl group, halogen-substituted phenyl group, C1-C4 alkoxy group-substituted phenyl group, or C1-C4 haloalkoxy group-substituted phenyl group.

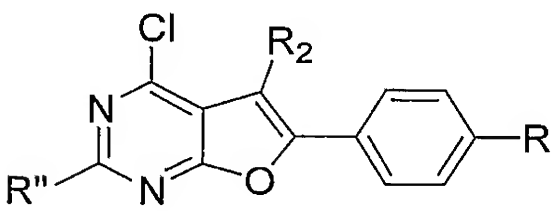
The compound represented by the Chemical Formulas 1, 2, 3 and 4 can exist in a free base or in an acid-addition salt such as chloride, sulfuric acid, citric acid or fumaric acid.

In addition, the present invention furovides an intermediate of the furopyrimidine compounds shown in formulas 1 to 4 defined by the following Chemical Formulas XI and XII, which inhibit tyrosine kinase activity of DDR2 protein, and its precursor and its pharmaceutically acceptable salt:

[Chemical Formula XI]



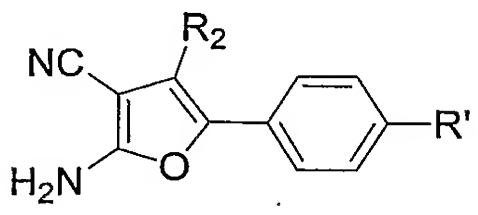
[Chemical Formula XII]



wherein, the definitions of the substitutions are as same as defined above. Moreover, a Reaction Formula and a Table shown below represents the compound defined in formulas XI and XII having hydrogen for R" is each shown in Figures VI and VII.

The compound in the present invention can be composed from compounds expressed by following Chemical Formula IV:

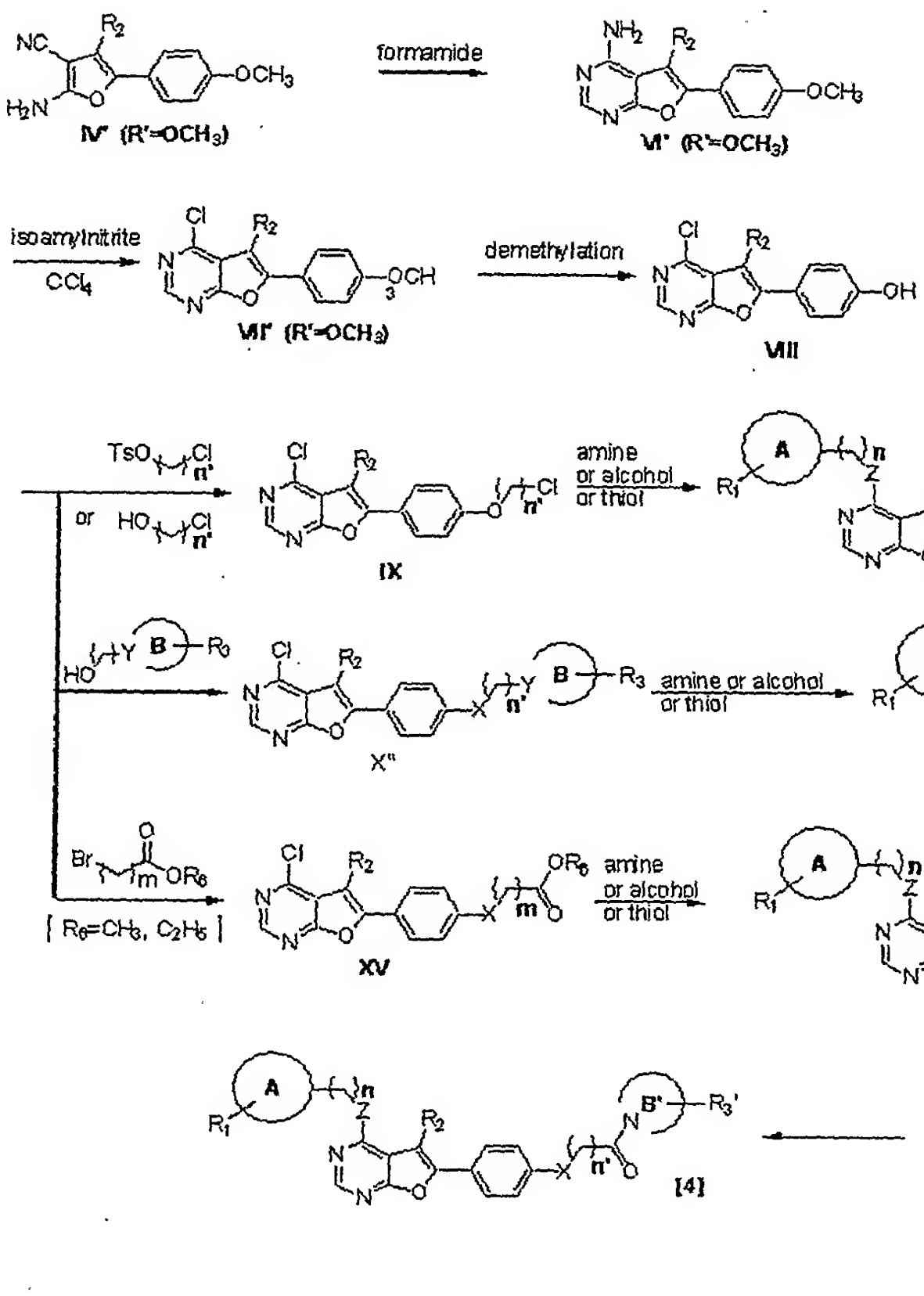
[Chemical Formula IV]



In case of the compound of Chemical Formula 2, since the substituent R' of Chemical Formula IV must generate a functional group that can be substituted by a substituent defined by Chemical Formula 5, it is preferred that R' is hydrogen, halogen, cyano, nitro, hydroxy, amino, CO2H, COHN2, CSNH2, amidine, C1-C4 alkyl group, C1-C4 haloalkyl group, C1-C7 alkoxy group, C1-C4 alkylamino group, C1-C4 alkylthio group, C1-C4 alkylamide group, C1-C4 acylamino group, C1-C4 acyloxy group or C1-C4 alkylsulfoneamide group.

For example, the compounds of Chemical Formula 2 and Chemical Formula 4 can be produced by the following Reaction Formula 1 by using a compound (IV') of the Chemical Formula IV, whose R' is $-OCH_3$, as a starting material:

[Reaction Formula 1]



wherein, Z is O, S or NH,

X is O, S or NH,

Y is C or N,

n is an integer between 0 and 4,

n' is an integer between 0 and 4,

m Is an integer between 0 and 4,

R_1, R_3 and R_3' are independently identical or different to each other, and may be single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, amidine, C1-C4 alkyl group, C1-C4 halo alkyl group, C1-C7 alkoxy group, C1-C4 alkyl amino group, C1-C4 alkylthio group, C1-C4 alkyl amide group, C1-C4 acyl amino group, C1-C4 acyl oxy group, C1-C4 alkyl sulfoneamide group, C1-C4 alkyl sulfonate group, imidic acid C1-C4 alkyl ester, thioimidic acid C1-C4 alkyl ester, hydroxy or amino, morpholine, acetate, acetamide, methanesulfoneamide group-substituted methyl group, C1-C4 halo alkyl group, C1-C4 alkoxy group, or a halogen-substituted benzyl oxy group,

A ring indicates benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, cyclo hexyl, piperidine or morpholine, and

R_2 indicates hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C5 alkyl group, C1-C5 haloalkyl group, alkylester, phenyl group, halogen-substituted phenyl group, or C1-C4 haloalkoxy group-substituted phenyl group.

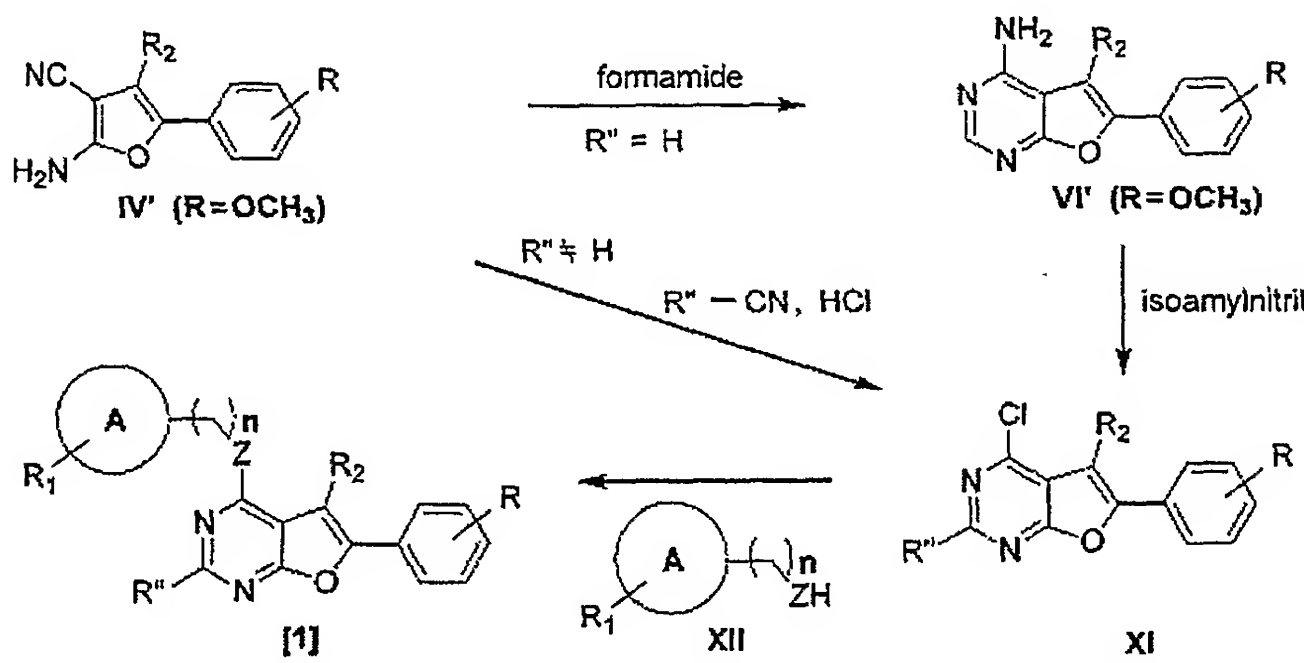
Reaction Formula 1 is one example for preparing the compound of Chemical Formula 2 and the compound of Chemical Formula 4, and the compounds can be produced by using compounds other than those illustrated (IV) in Reaction Formula 1 or without undergoing the process of producing the compound of VII' by adding isoamylnitrite and CCl_4 and then substituting –NH2 with –Cl to the compound VI', but rather, $-OCH_3$ of the compound VI' can be demethylated for the reaction to occur.

In addition, as for the compound of the Chemical Formula 1 or 3, since R'

of the compound VI is maintained until the final compound, the compound (IV") of Chemical Formula IV having the same R' as R can be used to produce it.

For example, the compound of Chemical Formula 1 can be produced by the following Reaction Formula 2:

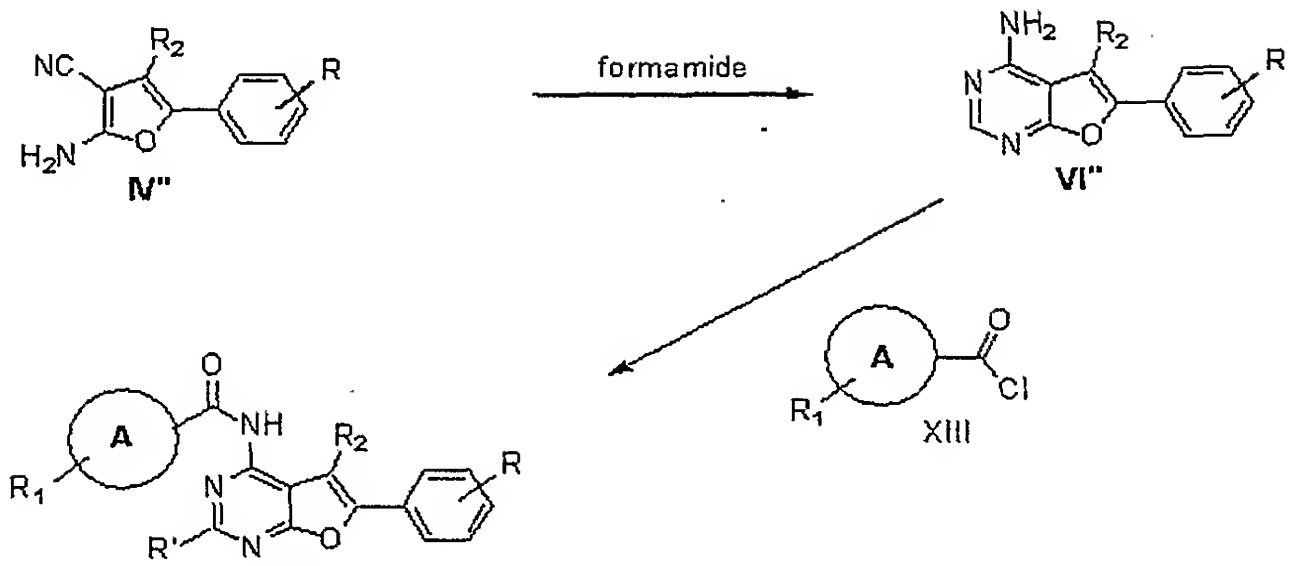
[Reaction Formula 2]



As stated above, Reaction Formula 2 is one example for producing the compound of Chemical Formula 1, and it can be produced by reacting the compound VI" with the compound XII by adding isoamylnitrite and CCl_4 without substituting $-NH_2$ of the compound VI" with –Cl.

In addition, the compound of Chemical Formula 3 can be produced by the following reaction Formula 3:

[Reaction Formula 3]



In Reaction Formulas 2 and 3 above, Z is O, S or NH,

R_1 is single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, amidine, C1-C4 alkyl group, C1-C4 halo alkyl group, C1-C7 alkoxy group, C1-C4 alkyl amino group, C1-C4 alkylthio group, C1-C4 alkyl amide group, C1-C4 acyl amino group, C1-C4 acyl oxy group, C1-C4 alkyl sulfoneamide group, C1-C4 alkyl sulfonate group, imidic acid C1-C4 alkyl ester, thioimidic acid C1-C4 alkyl ester, hydroxy or amino, morpholine, acetate, acetamide, methanesulfoneamide group-substituted methyl group, C1-C4 halo alkyl group, C1-C4 alkoxy group, or a halogen-substituted benzyl oxy group,

A ring indicates benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, cyclo hexyl, piperidine or morpholine,

R_2 indicates hydrogen, halogen, cyano, nitro, hydroxyl, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C5 alkyl group, C1-C5 haloalkyl group, alkylester, phenyl group, halogen-substituted phenyl group, C1-C4 alkoxy group-substituted phenyl group, or C1-C4 haloalkoxy group-substituted phenyl group, and

R may be single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C4 alkyl group, amidine, C1-C4 haloalkyl group, C1-C7 alkoxy group, C1-C4 alkylamino group, C1-C4 alkyl thio group, C1-C4 alkyl amide group, C1-C4 acylamino group, C1-C4 acyloxy group, or C1-C4 alkylsufoneamide group.

In Reaction Formula 2, n means an integer between 0 and 4.

In the Example of the present invention, the compound of Chemical Formulas 1, 2, 3 and 4 can be a compound of the numbers 5 ~ 132 of Table 6-1 as shown below.

The present invention also furovides a DDR2 tyrosine kinase activity inhibitor which contains a medically effective amount of one or more of the new furopyrimidine derivatives having an effect of inhibiting activity of DDR2 tyrosine kinase expressed by Chemical Formulas 1, 2, 3, 4, XI, XII and its pharmaceutically acceptable salts as an effective ingredient.

In addition, the present invention, as an effective ingredient, furovides for a remedial agent for treating diseases related to DDR2 tyrosine kinase activity such as liver cirrhosis or rheumatism that contains a medically effective amount of one or more of the new furopyrimidine derivatives and its pharmaceutically acceptable salts.

The pharmaceutical composition of the present invention can additionally include pharmaceutically acceptable carrier or excipient. As shown in Table 11 below, it was confirmed that the compounds of Chemical Formulas XI and XII, as well as the compounds of Chemical Formula 1 to 4, which are the end products, also exhibit excellent DDR2 tyrosine kinase inhibiting activity. Thus, the pharmaceutical composition of the present invention can include the compounds

of Chemical Formulas XI and/or XII as an effective ingredient.

As mentioned above, the DDR2 protein is a receptor protein that exhibits tyrosine kinase activity and includes a tyrosine kinase activity portion at its c-end. Using a DNA recombination technique and baculovirus expression technique, a protein that exhibits tyrosine kinase activity at the c-end portion (amino acid 441-825), which is a portion exposed to cytoplasm and is over-expressive in an insect cell, can be obtained. In addition, by inducing and thereby deforming tyrosine phosphorylation in various ways at the kinase activity portion, the kinase activity can be increased (refer to Korean Patent Application No. 2002-0067233, entitled "Deformed DDR2 Tyrosine Kinase Active Protein" and Korean Patent Application No. 2003-0076967 entitled "Deforming Method of DDR2 Tyrosine Kinase Activity and DDR2 Protein having the Deformed Kinase Activity using the Same Method").

The inhibiting activity of the compound of the present invention with respect to the DDR2 protein having the tyrosine kinase activity was measured. The tyrosine kinase activity of the tyrosine kinase activity portion of the DDR2 protein can be measured in various ways. For example, as a peptide substance, poly(D4Y)n attached with biotin furovided by Promega Co. can be used, a histone H2B protein can be used to measure, or the degree/amount of self-phosphorylation in the tyrosine kinase activity portion of the DDR2 protein can be measured. Using the movement of a phosphate group from an ATP being a substance for kinase activity to another peptide substance, the degree of activity can be measured by marking the gamma position of the phosphate group of the ATP with a ^{32}P isotope and then detecting the amount of ^{32}P radioactivity of the peptide substance.

As for the DDR2 tyrosine kinase inhibiting activity of the compound of the

present invention, the density of each compound inhibiting 50 % of the DDR2 tyrosine kinase activity is defined by IC_{50} value of each compound, which is as shown in Table 11. As shown in Table 11, the compounds expressed by Chemical Formulas VI and VII as well as Chemical Formulas 1, 2 and 3 all have the IC_{50} value below 500uM and an excellent tyrosine kinase inhibiting capability of DDR2 protein.

The compounds of the present invention are competitively joined with ATP, which is one of the DDR2 kinase substance, to exhibit the inhibiting effect. In order to confirm the fact that a representative compound 100 (Table 6) of the compounds of the present invention inhibits the DDR2 kinase activity by the ATP competition mechanism, the compound was processed in the density of 0uM, 0.2uM and 1.2uM and a reaction speed was obtained while changing the amount of ATP before illustrating its recifurocal plotting result as shown in Figure 1. As shown in Figure 1, the recifurocal plotting result shows that there is a meeting point on the Y-axis and changes in the intercept point on the X-axis, which indicates the inhibition of the DDR2 kinase activity.

Therefore, according to the tyrosine kinase inhibiting activity of the DDR2 protein, the compound of the present invention can be used as a remedial agent of various illnesses related to the tyrosine kinase activity of the DDR2 protein.

In addition, it has been found that increase in the tyrosine kinase activity of the DDR2 acceptor protein in hepatic stellate cells is related to the increase in number of cells. Based on this fact, various experimentations have been performed to verify the effect of inhibiting the growth and activity of the hepatic stellate cells when the compounds of the present invention are treated during the cultivation of the hepatic stellate cells, and the following results were obtained.

Figure 2 illustrates inhibiting of tyrosine phosphorylation of the DDR2 protein induced by a first type collagen in an HSC T6 cell, a hepatic stellate cell modem with an activated compound. The compound (100 of Table 6) is processed in a density of 5uM to 20uM for 24 hours and a tyrosine phosphorylation degree of the DDR2 protein of the HSC T6 cell was measured by Western blotting using a phosphorylated tyrosine specific antibody, and its results are shown. As shown in Figure 2, tyrosine phosphorylation of DDR2 protein induced by the first type collagen, which is the active ligand of the DDR2 receptor, is dependently reduced by the density of the treatment.

Figure 3 shows that the compounds of the present invention selectively inhibits the growth of HSC T6 cell which is determined by the SRB assay for detecting cell growth inhibiting effect. In the present invention, when the representative compound (100) of Table 6 is treated for 48 hours, the cell viability of HSC T6, which has been found to express the activated DDR2 tyrosine kinase, is shown to be reduced compared with rat2 fibroblast (-▼-) or HT1080 cell (..o..). As shown in Figure 3, with respect to the cells that express DDR2, the compounds of the present invention selectively work by specific inhibition of the DDR2 kinase activity.

Meanwhile, it is known that the number of hepatic stellate cells is increased and become active at the same time in case of liver cirrhosis. The active hepatic stellate cells increase generation of smooth muscle actin protein with an MMP-2 together with collagen. For this reason, inhibiting and eliminating the activity of the active hepatic stellate cells in liver cirrhosis is a major target to achieve a remedial effect.

In order to confirm that the compounds of the present invention reduces

generation of smooth muscle actin protein, the characteristics of the hepatic stellate cells, in the present invention, the representative compound (100) of Table 6 was treated in HSC T6 cell, namely, in a model of the activated hepatic stellate cells, for 24 hours, and cell cultivation solution was used to measure an amount of generated MMP-2 using ELISA assay. Its results are as shown in Figure 4A. More particularly, the cell cultivation solution was condensed by 20 times before the protein was attached to 96 well Maxi-Sorp plate, then it was masked by using a 5% skim milk solution followed by reacting with an MMP-2 specific antibody before washing it. Then, the amount of the attached MMP-2 antibody was quantitatively measured through a general peroxidase color development reaction using peroxidase-attached secondary antibody. As shown in Figure 4A, generation of MMP-2 was inhibited in proportion to the compound treatment density.

In addition, in order to confirm the effect of the reduction in generation of the smooth muscle actin protein, another feature of the activated hepatic stellate cells of the compounds of the present invention, the representative compound (100) of Table 6 of the present invention was processed in HSC T6 cells, namely, the active hepatic stellate cell model, for 24 hours, the cell was collected then was melted in a 1x lameli buffer solution before it was western-blotted by using the smooth muscle specific antibody to measure change in the amount of the smooth muscle actin protein according to the compound treatment. Its result is shown in Figure 4B. As shown in Figure 4B, generation of the smooth muscle actin protein was reduced in proportion to the compound treatment density.

Moreover, the compounds of the present invention is found to induce apoptosis of active hepatic stellate cells, confirming an excellent remedial effect

with respect to liver cirrhosis. In order to confirm the fact that the compounds of the present invention substantially induces apoptosis of the hepatic stellate cell by inhibiting the DDR2 kinase activity, the compound (Table 6, Number 100) of the present invention was treated to HSC T6 cell, namely, the hepatic stellate cell, for 24 hours, and a gene-segmentation phenomenon of the entire genome DNA was observed. Its results are as shown in Figure 5.

As noted in Figure 5, when the compounds of the present invention were treated, the segmentation effect of DNA was largely observed at a high density of 30uM, thus showing a remedial effect of the compounds of the present invention with respect to liver cirrhosis by effectively eliminating the active hepatic stellate cells.

As mentioned above, the compounds of the present invention inhibit the growth and the activity of the hepatic stellate cells, which are the main causes of liver cirrhosis, reduce generation of the MMP-2, which is a feature of an active hepatic stellate cell and the smooth muscle actin protein, and induce apoptosis, thus furoviding an excellent treatment effect for liver cirrhosis.

In addition, the compound of the present invention inhibits accumulation of collagen in a liver tissue causing liver fibrosis which is the main cause of liver cirrhosis, thereby treating liver cirrhosis. In order to confirm the effect of inhibiting accumulation of collagen in the liver tissue, a liver cirrhosis animal model for bile duct suture was made by using a whistar rat aged 7 weeks, and the compound of the present invention (the number 100 of Table 6) of the present invention was injected intravenously by the amount of 10mg/kg, one time per day for two weeks through tail intravenous injections. After the bile duct suture operation, it was divided into a group in which the compound was injected and another group

(reference group) in which the compound is not injected to measure their amount s of hydroxyl praline in their liver tissue. The results were shown in Table 12, which also shows the measured value from the group that did not undergo the bile duct suture operation.

Hydroxy proline seldom exists in any other proteins in a human body and is amino acid constituting collagen. In the present invention, it is an index for directly indicating the amount of collagen in the liver tissue, and the amount of hydroxyl proline of the liver tissue was measured.

As shown in Figure 12, the amount of hydroxy proline measured in the group in which the compound of the present invention was not injected after the bile duct suture operation was higher, by about 2.5 times, than that of the group which did not undergo the bile duct suture operation. This shows that collagen was considerably accumulated in the liver tissue due to the bile duct suture and the liver cirrhosis pathogenic effect had been developed. Meanwhile, compared with the group which was left for two weeks after the bile duct suture operation, the group in which the compound of the present invention was injected showed that there was an increase of the amount of the hydroxyl proline in the liver tissue, which is a considerable alleviation.

Such results show that the compound of the present invention inhibits accumulation of collagen in the liver tissue as well as increase and activity of the hepatic stellate cell, so that it has an anti-fibrosis effect with respect to liver cirrhosis. Thus, the excellent liver cirrhosis treatment effect of the compound of the present invention is shown again.

Figure 6 shows the comparing results of the liver tissues from the rats administered with the representative compound 100 (Table 6) of the present

invention, the rats that were injected with only carriers, and the rats to which the bile duct suture operation was not performed, all of which were made into respective freeze dehydration sections, and then the sections were stained with Masson stain. The results confirm that the deposition of collagen was reduced because of the compound of the present invention.

As shown in Figure 6, the liver tissue from the rat, into which the compound of the present invention was injected after the bile duct suture operation was performed, showed considerably reduced amount of collagen, which was dyed in blue color, when compared to that of the rat into which only the carrier was injected. Similar to the liver tissue of the rats from the reference group, the deposition of collagen was hardly observed.

The compound of the present invention also has an excellent inhibiting effect for an arthritis pathogenic factor such as rheumatism. One cause of arthritis such as rheumatism is activation and excessive furoliferation of synovial cell of synovium. The activated synovial cells excessively secrete MMP-1 proteins, thereby destroying collagen proteins constituting cartilage tissues to make the rheumatism serious.

Recently, it has been observed that there is an increase in the expression of the DDR2 protein in the synovial cell in case of the rheumatism. When the synovial cell is a type of fibrotic cells like the hepatic stellate cell, it can be inferred that expression of DDR2 in the synovial cell, like the hepatic stellate cell, is the cause of the disease.

In order to verify that the compound of the present invention inhibits the growth of the synovial cells, the compound (100 of Table 6) of the present invention was processed in a synovial fibroblast extracted from a rheumatism

patient for 48 hours according to each density, and then, the number of living cells was compared with the number of cells before the treatment with the compound was performed through the SRB assay to obtain a % cell viability rate as shown in Figure 7.

As shown in Figure 7, the cell viability of the synovial fibroblast is reduced in proportion to the density of the compound of the present invention. This shows that the compound of the present invention, which is an inhibiting material specific for the DDR2 kinase activity, inhibits the growth and the activity of the synovial fibroblast, which is the cause of the rheumatism, thereby having a remedial effect for rheumatism.

In addition, since the compound of the present invention expresses inhibiting activity of the MMP-1 (matrix metalloproteinase-1) in the synovial fibroblast, it has a treatment activity of arthritis. Figure 8 shows that a commonly-used Northern blotting was performed on the synovial fibroblast processed with the representative compound (100 of Table 6) of the present invention and an MMP-1 m-RNA was quantitatively measured. Moreover, it is also shown that MMP-1 expression in the synovial fibroblast was considerably inhibited by the compound of the present invention. This fact verifies that the compound of the present invention is usable as a treatment for rheumatism according to its inhibition of the kinase activity of the DDR2, and that the compound of the present invention can also be used as a treatment for a malignant tumor by inhibiting expression of the MMP-1 based on the fact that the activity of the MMP-1 is critical for spread of various cancers. A study entitled “Identificatin of genes cell lines associated with the invasive status of human mammary carcinoma cell lines by transcriptional furofiling” by Vesna Evtimova et al., 189-198 pages, 24

volume, 2003, in "Tumor Biology" supports the above-mentioned fact. The study shows that the amount of expression of DDR2 gene is closely related to the cancer cell strains that has a high spreading activity.

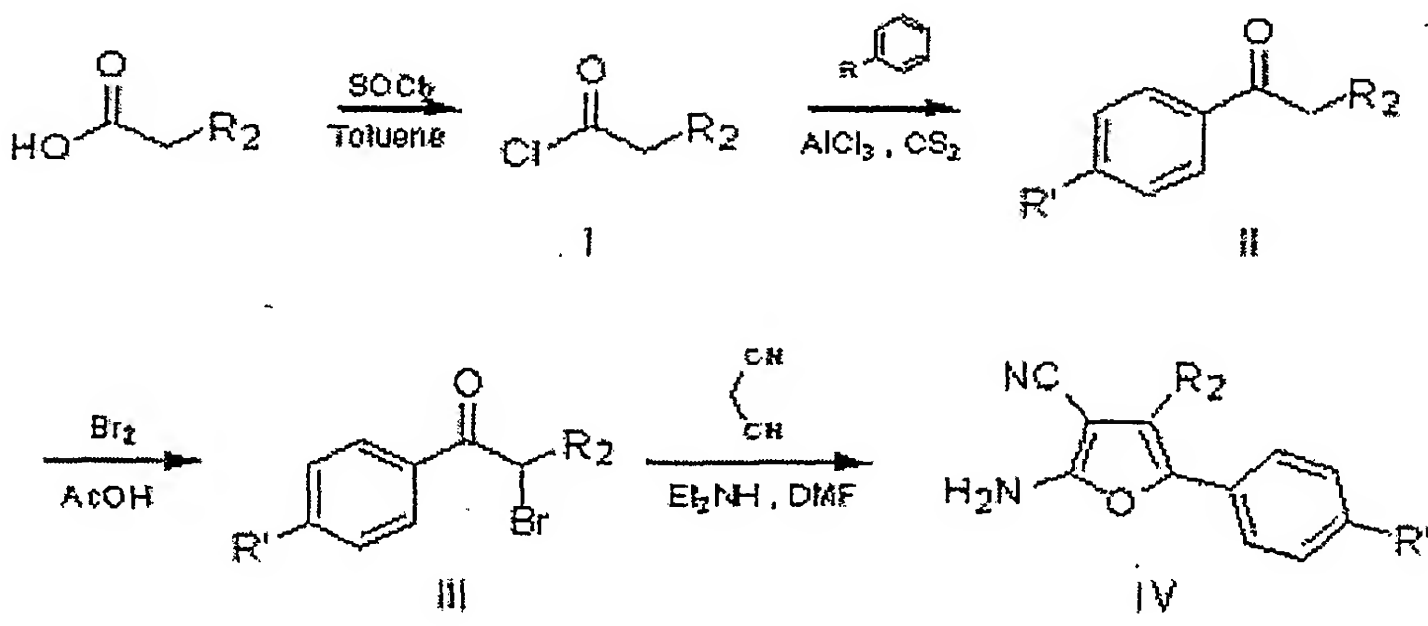
The compound, its preparation method and its biological activity in the present invention will now be described in detail through preferred Examples, but the present invention is not limited thereto. Some characteristic compound preparation methods are taken as examples in the following Examples, but except for those, compounds of the present invention will be easily prepared by a person who skilled in the art where the present invention pertains based on the methods described in the following Examples.

[Example]

I. Preparation of a Compound of the Present Invention

Compounds I, II, III and IV were prepared by a preparation process of the below Reaction Formula 4:

Reaction Formula 4



Example 1: Preparation of 4-methoxy-phenyl-acetyl chloride (compound I)

16.62g (0.1 mol) of 4-methoxyphenylacetic acid was dissolved in 10ml of benzene before 29ml (0.2 mol) of thionylchloride was added thereto. Then, the solution was heated and refluxed, and was stirred for one hour. Thionylchloride remaining in the reaction solution and the solvent was condensed to be removed to obtain 4-methoxy-phenyl-acetyl chloride (compound I), a liquid phase product, at a quantitative yield. The product was used without purification.

Example 2: Preparation of 1-phenyl-2-(4-methoxyphenyl) ethanone (compound II)

200ml of dichloromethane was added to 40g (0.3mol) of aluminum (III) chloride and was stirred, into which a material obtained by diluting 29.5ml (0.33 mol) of benzene and the 18.5g (0.1mol) of 4-methoxy-phenyl-acetyl chloride obtained from Example 1 in 100ml of dichloromethane (CH2Cl2) was slowly added for about 30 minutes and then stirred at a room temperature for two hours. The resulting reaction solution was added to a 400ml of 1M hydrochloric acid aqueous solution, from which an organic layer was extracted, dried, condensed, and purified by column chromatography to obtain a light yellow solid form of 1-phenyl-2-(4-methoxyphenyl)ethanone (compound II). And a compound of 1-(4-toryl)-2-(4-methoxyphenyl)ethanone and 1-(4-toryl)-2-(4-cyanophenyl)ethanone, 1-(4-methoxyphenyl)-2-phenylethanone,1-(4-methoxyphenyl)-2-(4-chlorophenyl)ethanone using the same method.

Example 3: Preparation of alpha-bromoketone-based compound (compound III)

(1) 2-bromo-4'-chlorofuropiophenone (compound IIId)

50ml of acetic acid was added dropwiselyly to 16.86g of 4'-chlorofuropiophenone and was cooled at 0°C before 5.14ml (0.1 mol) of brome was slowly added dropwiselyly. The resultant mixture was stirred at a room temperature for two hours, to which 270ml of water was added, filtered, washed with a sufficient amount of water and then dried to obtain a white solid product of 24.13g of 2-bromo-4'-chlorofuropiophenone(IIId). Compounds IIIf and IIIi, a compound IIIk, a compound IIII, compounds IIIn and IIIu, and a compound IIIx of Table 1 shown below were also each obtained using the same method.

(2) 2-bromo-4'-methoxyfuropiophenone (compound IIIe)

450ml of dioxane was added dropwisely to 32.84g (0.2 mol) of 4-methoxyfuropiophenone and 89.34g (0.4 mol) of $CuBr_2$, which was then heated and refluxed for six hours. The resultant mixture was cooled at a room temperature to remove dioxane, water was applied thereto, from which an organic layer was extracted with ethylacetate twice or three times. The obtained organic layer was dried, condensed and re-crystallized with n-hexane to obtain an light yellow solid product of 48.62g of 2-bromo-4'-methoxy furopiophenone (IIIe). A compound IIIy as shown in Table 1 below was also obtained using the same method.

(3) 2-bromo-1-(4'-chlorophenyl)-3-methyl-1-butanone (compound IIIm)

14ml of carbon disulfide was added dropwisely to 1.02ml of chlorobenzene, and then 1.6g (12 mmol) of aluminum(III)chloride was added thereto, which was then heated and refluxed. A solution obtained by dissolving

1.46ml (10 mmol) of isobarerilchloride in 2ml of carbondisulfide was slowly added to the resultant mixture for about 30 minutes and then was heated for six hours, and was cooled at a room temperature to be condensed. 1M hydrochloric acid aqueous solution was added to the resulting reaction solution, from which an organic layer was extracted with dethyletere twice or three times. The organic layer was washed with 10% sodium hydroxide aqueous solution, dried, condensed, and then, purified by column chromatography to obtain a white solid product of 1.85g of 1-(4'-chlorophenyl)-3-methyl-1-butanone.

^{1}H NMR (400 MHz DMSO-d_6) δ 7.89 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 2.81 (d, J = 6.8 Hz, 2H), 2.36~2.20 (m, 1H), 0.99 (d, J = 6.4 Hz, 6H)

14ml of ethylacetate and 14ml of chloroform were added dropwisely to the previously obtained 1.85g (9.4 mmol) of 1-(4'-chlorophenyl)-3-methyl-1-butanone and 2.1g (9.4 mmol) of $CuBr_2$,then the solution was heated and refluxed for two hours. The resultant mixture was cooled at a room temperature to remove solids, and then, the filtrate was dried and condensed to obtain a white solid product of 2-bromo-1-(4'-chlorophenyl)-3-methyl-1-butanone (IIIm).

(4) 2-bromo-4'-phenoxyfuropiophenone (compound IIIj)

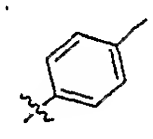
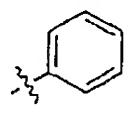
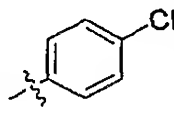
100ml of dimethylanilene was added dropwisely to 13.2 ml (150 mmol) of phenol, 16.6 g (120 mmol) of potassium carbonate (K_2CO_3) and 19.4 ml (140 mmol) of 4'-fluorofuropiophenone, and then was heated and refluxed for four hours. The resultant mixture was cooled at a room temperature and water was added thereto, from which an organic layer was extracted with diethylether twice or three times. The obtained organic layer was dried, condensed, and then, purified by column chromatography to obtain 27.6g of white solid product of 4'-phenoxyfuropiophenone.

^{1}H NMR (400 MHz DMSO-d_6) δ 7.99 (d, J = 8.8 Hz, 2H), 7.49~7.43 (m, 2H), 7.28~7.22 (m, 1H), 7.15~7.10 (m, 2H), 7.04 (d, J = 8.8 Hz, 2H), 3.00 (q, J = 6.8 Hz, 2H), 1.07 (t, J = 6.8 Hz, 3H)

11.3g (50 mmol) of the above-obtained 4'-phenoxyfuropiophenone and 50 mg (0.4 mmol) of aluminum (III) chloride were added to 20 ml of diethylether and then was cooled at 0°C, to which brome was slowly added dropwisely. The resultant mixture was stirred for three hours at the same temperature and water was added thereto, from which an organic layer was extracted with diethylether, and then was dried, condensed, and then, re-crystallized with n-hexane to obtain 2-bromo-4'-phenoxyfuropiophenone (IIIj).

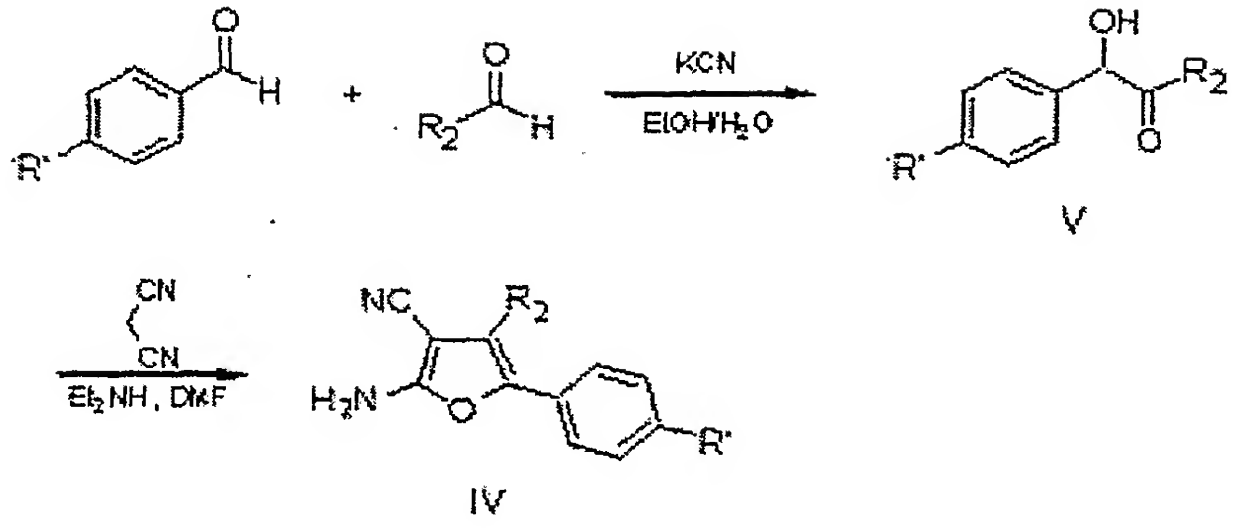
The following table 1 shows the analysis results of the alpha-bromo ketone-based compounds IIId to IIIy obtained in the Example 3.

[Table 1]

	R'	R_2	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)	Yield (%)
IIId	Cl	CH_3	7.97 (d, J = 9.2 Hz, 2H), 7.46 (d, J = 9.2 Hz, 2H), 5.23 (q, J = 6.8 Hz, 1H), 1.90 (d, J = 6.8 Hz, 3H)	97
IIIe	OCH_3	CH_3	8.03 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 5.79 (q, J = 6.4 Hz, 1H), 3.87 (s, 3H), 1.77 (d, J = 6.4 Hz, 3H)	98
IIIf	CH_3	CH_3	7.94 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 5.79 (q, J = 6.8 Hz, 1H), 2.38 (s, 3H), 1.76 (d, J = 6.8 Hz, 3H)	79
IIIg	F	CH_3	^{1}H NMR (400 MHz $CDCl_3$) δ 8.08~8.05 (m, 2H), 7.18~7.14 (m, 2H), 5.24 (q, J = 6.4 Hz, 1H), 1.91 (d, J = 6.4 Hz, 3H)	67
IIIh	I	CH_3	^{1}H NMR (400 MHz $CDCl_3$) δ 7.86 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 5.21 (d, J = 6.4 Hz, 1H), 1.89 (d, J = 6.4 Hz, 3H)	40
IIIi	Br	CH_3	7.98 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 5.82 (q, J = 6.4 Hz, 1H), 1.79 (d, J = 6.4 Hz, 3H)	98
IIIj	OPh	CH_3	8.07 (d, J = 8.4 Hz, 2H), 7.58~7.40 (m, 2H), 7.32~6.98 (m, 5H), 5.78 (q, J = 6.4 Hz, 1H), 1.77 (d, J = 6.4 Hz, 3H)	76
IIIk	SCH_3	CH_3	7.94 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 5.25 (q, J = 6.8 Hz, 1H), 2.53 (s, 3H), 1.89 (d, J = 6.8 Hz, 3H)	57
IIIl	Cl	Et	^{1}H NMR (400 MHz $CDCl_3$) δ 7.96 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 5.50 (t, J = 6.4 Hz, 1H), 2.23~2.13 (m, 2H), 1.09 (t, J = 7.6, 3H)	40
IIIm	Cl	$CH(CH_3)_2$	8.08 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 5.62 (d, J = 8 Hz, 1H), 2.20~2.06 (m, 1H), 1.11 (d, J = 6.4 Hz, 3H), 0.99 (d, J = 6.4 Hz, 3H)	64
IIIn	Cl	Ph	8.10 (d, J = 8.4 Hz, 2H), 7.72~7.24 (m, 7H), 7.20 (s, 1H)	95
IIIu	OCH_3		^{1}H NMR (400 MHz $CDCl_3$) δ 7.97 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.36 (s, 1H), 3.85 (s, 3H), 2.33 (s, 3H)	99
IIIx	OCH_3		^{1}H NMR (400 MHz $CDCl_3$) δ 7.97 (d, J = 8.8 Hz, 2H), 7.55~7.49 (m, 2H), 7.37~7.24 (m, 3H), 6.88 (d, J = 8.8 Hz, 2H), 6.38 (s, 1H)	93
IIIy	OCH_3		^{1}H NMR (400 MHz $CDCl_3$) δ 7.97 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.31 (s, 1H), 3.85 (s, 3H)	87

A starting material IV was prepared by the following Reaction Formula 5:

[Reaction Formula 5]



Example 4: Preparation of alpha-hydroxyketone-based (compound V) compound

(1) Preparation of 4,4'-dichlorobenzoin (Vv)

120 ml of ethyl alcohol was added dropwisely to 14 g (0.1 mol) of chlorobenzaldehyde, to which 14.98 g (0.23 mol) solution obtained by dissolving potassium cyanide (KCN) in 10 ml of water was slowly added, and heated and refluxed for 12 hours. The resultant mixture was cooled at a room temperature and water was added thereto, which was then filtered, dried and then re-crystalized or purified by column chromatography to obtain a light yellow solid product of 4,4'-dichlorobenzoin (Vv).

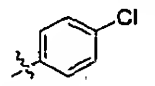
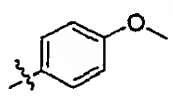
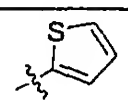
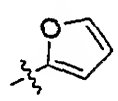
(2) Preparation of 2-hydroxy-2-phenyl-(4-methoxy)acetophenone (Vx)

1.36 g (2 mmol) of anizaldehyde and 30ml of saturated KCN aqueous solution were added to a solution obtained by applying 50 ml of ethylalcohol to dissolve 2.12 g (10 mmol) of benzoin, heated and refluxed, and then, stirred for three hours. Water was applied to the reaction solution, from which an organic layer was extracted with ethylacetate twice and three times, dried, condensed and then purified by column chromatography to obtain a light yellow solid product

of 2-hydroxy-2-phenyl-(4-methoxy) acetophenone (Vx). Compounds Vq and Vr of table 2 shown below were also each obtained using the same method.

Table 2 shows analysis results of the alpha-hydroxyketone-based compounds Vv to Vr obtained in Example 4.

[Table 2]

	R'	R_2	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)	Yield (%)
Vv	Cl		8.03 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 6.31 (d, J = 6.0 Hz, 1H), 6.09 (d, J = 6.0 Hz, 1H)	12
Vx	H		^{1}H NMR (400 MHz $CDCl_3$) δ 7.91 (d, J = 8.8 Hz, 2H), 7.39~7.24 (m, 5H), 6.86 (d, J = 8.8 Hz, 2H), 5.89 (d, J = 6.4 Hz, 1H), 4.66 (d, J = 6.4 Hz, 1H), 3.82 (s, 3H)	17
Vq	H		^{1}H NMR (400 MHz $CDCl_3$) δ 7.64~7.62 (m, 2H), 7.42~7.31 (m, 6H), 7.50~7.28 (m, 1H), 5.74 (m, 1H)	13
Vr	H		7.99 (s, 1H),7.67~7.65 (m, 1H), 7.46 (d, J = 7.6 Hz, 2H), 7.35~7.31 (m, 2H), 7.27 (d, J = 7.6 Hz, 1H), 6.71~6.69 (m, 1H), 6.16~6.14 (m, 1H), 5.76~5.75 (m, 1H)	32

Example 5: Preparation of 2-amino-3-furonitril-based compound (compound IV)

(1) Preparation of 2-amino-3-cyano-5-(4-chlorophenyl)furan (IVa)

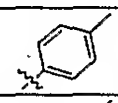
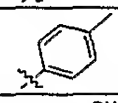
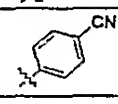
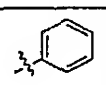
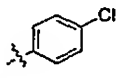
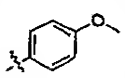
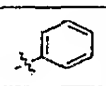
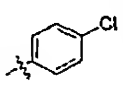
20 ml of dimethylformamide (DMF) was added dropwisely to the 11.67g (50 mmol) of 2-bromo-4'-chloroacetophenone(IIIa) obtained in Example 3 and 3.3 g (50 mmol) of malononitril (CH2((CN)2), which was then cooled at 0°C, and 15.5 ml (150 mmol) of diethylamine was slowly added thereto for about 30 minutes. At this step, the temperature of the reaction solution was controlled not to go beyond 40°C. And then, it was stirred at a room temperature for three hours, 60 ml of water was added thereto and filtered, which was washed sufficiently with water and n-hexane before being dried, and then, re-crystallized with ethylalcohol to obtain yellow-brown solid product of 2-amino-3-cyano-5-(4-chlorophenyl) furan (IVa). Compounds IVb to IVp and compounds IVs to IVu, IVx and IVy of Table 3 were also obtained using the same method.

(2) Preparation of 2-amino-3-cyano-4,5-di(4-chlorophenyl)furan (IVv)

15ml of dimethylformamide (DMF) was applied to the 7g (25 mmole) of 4,4'-diclorobenzoin(Vv) obtained in the Example 4 and 1.98g (30 mmol) of malononitril, which was then cooled at 0°C, and then, 100 mmol of diethylamine was slowly added dropwisely thereto for about 30 minutes. In this case, the temperature of the reaction solution was controlled not to go beyond 40°C. And then, it was stirred at a room temperature for 18 hours, 100 ml of water was added thereto and filtered, which was washed sufficiently with water and n-hexane and was dried, and then, re-crystallized with diethylether to obtain yellow-brown solid product of 2-amino-3-cyano-4,5-di(4-chlorophenyl)furan (IVv). Compounds IVq, IVr and IVw were also each obtained using the same method.

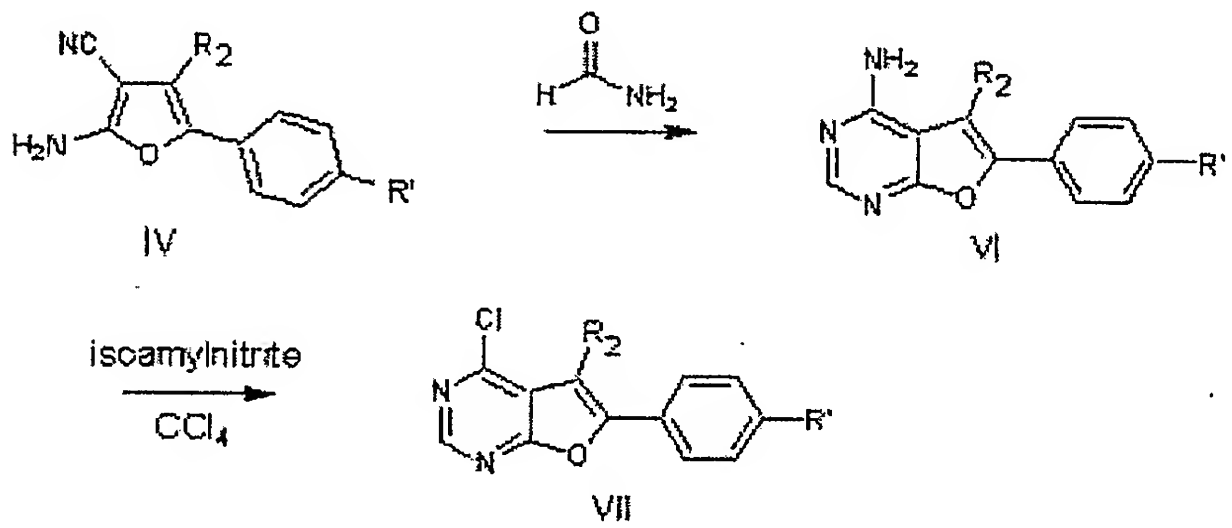
Table 3 shows analysis results of the obtained 2-amino-3-furonitril-based compounds IVa to Ivy.

[Table 3]

	R'	R_2	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)	Yield (%)
IVa	Cl	H	7.66~7.74 (br s, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.06 (s, 1H)	91
IVb	OCH_3	H	7.55~7.45 (br s, 2H), 7.41 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 6.79 (s, 1H), 3.75 (s, 3H)	67
IVc	CH_3	H	7.62~7.54 (br s, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.89 (s, 1H), 2.28 (s, 3H)	83
IVd	Cl	CH_3	7.67~7.61 (br s, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 2.15 (s, 3H)	90
IVe	OCH_3	CH_3	7.49~7.41 (br s, 2H), 7.36 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 3.77 (s, 3H), 2.11 (s, 3H)	84
IVf	CH_3	CH_3	7.54~7.43 (br s, 2H), 7.31 (d, J = 8 Hz, 2H), 7.20 (d, J = 8 Hz, 2H), 2.29 (s, 3H), 2.13 (s, 3H)	92
IVg	F	CH_3	7.60~7.49 (br s, 2H), 7.46~7.43 (m, 2H), 7.27~7.22 (m, 2H), 2.13 (s, 3H)	77
IVh	I	CH_3	7.73 (d, J = 8.4 Hz, 2H), 7.70 (s, 2H), 7.21 (d, J = 8.4 Hz, 2H), 2.15 (s, 3H)	89
IVi	Br	CH_3	7.68~7.62 (br s, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 2.15 (s, 3H)	82
IVj	OPh	CH_3	7.60~7.35 (m, 6H), 7.12~6.94 (m, 5H), 2.15 (s, 3H)	43
IVk	SCH_3	CH_3	7.62~7.42 (br s, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 2.48 (s, 3H), 2.15 (s, 3H)	87
IVl	Cl	Et	7.72~7.58 (br s, 2H), 7.46 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 2.93 (q, J = 7.6 Hz, 2H), 1.22 (t, J = 7.6 Hz, 3H)	91
IVm	Cl	$CH(CH_3)_2$	7.62~7.52 (br s, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 3.42~3.08 (m, 1H), 1.28 (d, J = 8.4 Hz, 6H)	47
IVn	OCH_3		7.64~7.54 (br s, 2H), 7.25 (s, 4H), 7.17 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 3.72 (s, 3H), 2.35 (s, 3H)	40
IVo	Cl		7.89~7.72 (br s, 2H), 7.35 (d, J = 8.8 Hz, 2H), 7.28 (s, 4H) 7.21 (d, J = 8.8 Hz, 2H), 2.36 (s, 3H)	47
IVp	Cl		7.90~7.80 (br s, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.42~7.41 (m, 4H) 7.37 (d, J = 8.8 Hz, 2H)	46
IVq	H		7.83~7.73 (br s, 2H), 7.67 (dd, J = 5.2, 0.8 Hz, 1H), 7.34~7.32 (m, 4H), 7.22 (dd, J = 3.6, 1.2 Hz, 1H), 7.17 (dd, J = 5.2, 3.6 Hz, 2H)	49
IVr	H		7.84~7.74 (br s, 2H), 7.77~7.76 (m, 1H), 7.44 (d, J = 7.2 Hz, 2H), 7.41~7.37 (m, 2H), 7.32~7.28 (m, 1H), 6.70 (d, J = 3.2 Hz, 1H), 6.64 (dd, J = 3.6, 3.2 Hz, 1H)	74
IVs	NO_2	CO_2Et	8.30 (d, J = 8.8 Hz, 2H), 8.15~8.05 (br s, 2H), 8.00 (d, J = 8.8 Hz, 2H), 4.30 (d, J = 7.8 Hz, 2H), 1.12 (t, J = 7.8 Hz, 3H)	86
IVt	H	Ph	7.37 (s, 2H), 7.49~7.38 (m, 5H), 7.29~7.19 (m, 5H)	86
IVu	Cl		7.85~7.75 (br s, 2H), 7.52~7.28 (m, 7H), 7.21 (d, J = 8.8 Hz, 2H).	89
IVv	Cl		7.88~7.82 (br s, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H)	68
IVw	OCH_3		7.64~7.54 (br s, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 3.80 (s, 3H), 3.72 (s, 3H)	84
IVx	OCH_3		7.56~7.64 (br s, 2H), 7.47~7.32 (m, 5H), 7.16 (d, J = 9.2 Hz, 2H), 6.86 (d, J = 9.2 Hz, 2H), 3.71 (s, 3H)	72
IVy	OCH_3		8.30 (s, 1H), 7.65 (s, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 3.71 (s, 3H)	69

4-amino furopyrimidine-based compound VI and 4-chloro furopyrimidine-based compound VII were prepared by using the compound IV obtained in Example 5 as a starting material as shown in Reaction Formula 6.

[Reaction 6]

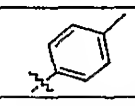
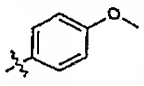
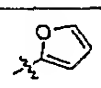
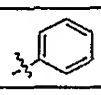
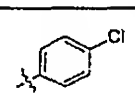
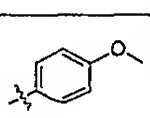
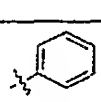
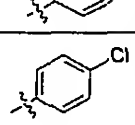


Example 6: Preparation of 4-amino furopyrimidine-based compound 4-amino-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (VIa)

20ml of formamide was applied dropwisely to the 4.37 g (20 mmol) of 2-amino-3-cyano-5-(4-chlorophenyl)furan (IVa) obtained in Example 5, which was heated and refluxed for 12 hours and then cooled at a room temperature. 100 ml of water was added thereto, and a generated solid was filtered, which was washed with water and n-hexane sufficiently, and then, dried. Thereafter, the resultant material was re-crystallized with acetone and ethylalcohol to obtain a brown-colored solid product of 4-amino-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (VIa). Compounds VIb to VIy of table 4 were also obtained, respectively, according to the same method.

Table 4 shows analysis results of the obtained 4-amino furopyrimidine-based compound VIa to VIy:

[Table 4]

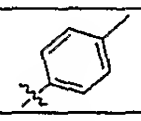
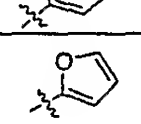
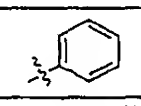
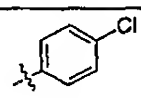
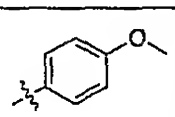
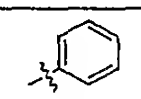
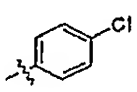
	R'	R_2	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)	Yield (%)
VIa	Cl	H	8.18 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.52~7.62 (m, 4H), 7.34 (s, 1H)	90
VIb	OCH_3	H	8.15 (s, 1H), 7.71 (d, J = 8 Hz, 2H), 7.48~7.42 (br s, 2H), 7.16 (s, 1H), 7.07 (d, J = 8 Hz, 2H), 3.84 (s, 3H)	75
VIc	CH_3	H	8.17 (s, 1H), 7.67 (d, J = 8 Hz, 2H), 7.52~7.42 (br s, 2H), 7.31 (d, J = 8 Hz, 2H), 7.25 (s, 1H), 2.37 (s, 3H)	75
VId	Cl	CH_3	8.17 (s, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 7.28~7.13 (br s, 2H), 2.51 (s, 3H)	91
VIe	OCH_3	CH_3	8.13 (s, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.20~6.89 (m, 4H), 3..81 (s, 3H), 2.48 (s, 3H)	67
VIf	CH_3	CH_3	8.15 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.18~7.06 (br s, 2H), 2.51 (s, 3H), 2.37 (s, 3H)	46
VIg	F	CH_3	8.16 (s, 1H), 7.76~7.73 (m, 2H), 7.38~7.36 (m, 2H), 7.26~7.10 (br s, 2H), 2.13 (s, 3H)	69
VIh	I	CH_3	8.14 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.17 (s, 2H), 2.61 (s, 3H)	70
VIi	Br	CH_3	8.17 (s, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.28~7.12 (br s, 2H), 2.51 (s, 3H)	83
VIj	OPh	CH_3	8.15 (s, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 1H), 7.48~7.40 (m, 1H), 7.26~7.02 (m, 7H), 2.51 (s, 3H)	96
VIk	SCH_3	CH_3	8.15 (s, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.22~7.04 (br s, 2H), 2.53 (s, 3H), 2.50 (s, 3H)	82
VIl	Cl	Et	8.18 (s, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.20~7.10 (br s, 2H), 2.93 (q, J = 7.2 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H)	85
VIm	Cl	$CH(CH_3)_2$	8.22 (s, 1H), 7.68~7.52 (br s, 4H), 7.04~6.88 (br s, 2H), 3.44~3.28 (m, 1H), 1.29 (d, J = 7.6 Hz, 6H)	89
VIn	OCH_3		8.24 (s, 1H), 7.39~7.37 (m, 6H), 6.93 (d, J = 8.8 Hz, 2H), 3.75 (s, 3H), 2.42 (s, 3H)	40
VIx	H		8.26 (s, 1H), 7.56~7.49 (m, 2H), 7.46~7.31 (m, 7H), 7.13 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H)	23
VIq	H		8.30 (s, 1H), 7.85 (dd, J = 5.2, 1.2 Hz, 1H), 7.59~7.50 (m, 4H), 7.45~7.37 (m, 4H), 7.31 (dd, J = 5.2, 3.2 Hz, 1H)	2
VIr	H		8.29 (m, 1H), 7.94 (t, J = 1.2 Hz, 2H), 7.61~7.59 (m, 7H), 6.70 (1s, 1H)	10
VIs	NO_2	CO_2Et	8.38~8.31 (m, 4H), 8.18~8.11 (m, 3H), 4.28 (q, J = 3.2 Hz, 2H), 2.65 (t, J = 3.2 Hz, 3H)	70
VIt	H	Ph	8.28 (s, 1H), 7.60~7.32 (m, 12H)	47
VIu	Cl		8.29 (s, 1H), 7.68~7.18 (m, 9H)	96
VIv	Cl		8.27 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H)	98
VIw	OCH_3		8.23 (s, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 3H)	89
VIx	OCH_3		8.25 (s, 1H), 7.60~7.46 (m, 5H), 7.36 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 3.75 (s, 3H)	90
VIy	OCH_3		8.25 (s, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 3.76 (s, 3H)	76

Example 7: Preparation of 4-chloro furopyrimidine-based compound 4-chloro-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (VIIa)

50ml of chloroform was applied dropwisely to the 7.37 g (30 mmol) of 4-amino-6-(4-chlorophenyl)-furo[2,3,d]pyrimidine (VIa) obtained in Example 6, and 8.6 ml (65.1 mmol) of isoamilnitrite was added thereto, which was then heated and refluxed for 14 hours. Thereafter, the resultant mixture was cooled at a room temperature, chloroform was removed therefrom under a decompressed pressure, which was then purified by column chromatography to obtain a yellow solid product of 4-chloro-t-(4-chlorophenyl)furo[2,3,d]pyrimidine (VIIa). Compounds of table 5 were also each obtain by using the same method.

Table 5 shows analysis results of the thusly-obtained 4-chloro furopyrimidine-based compounds VIIa to VIIy.

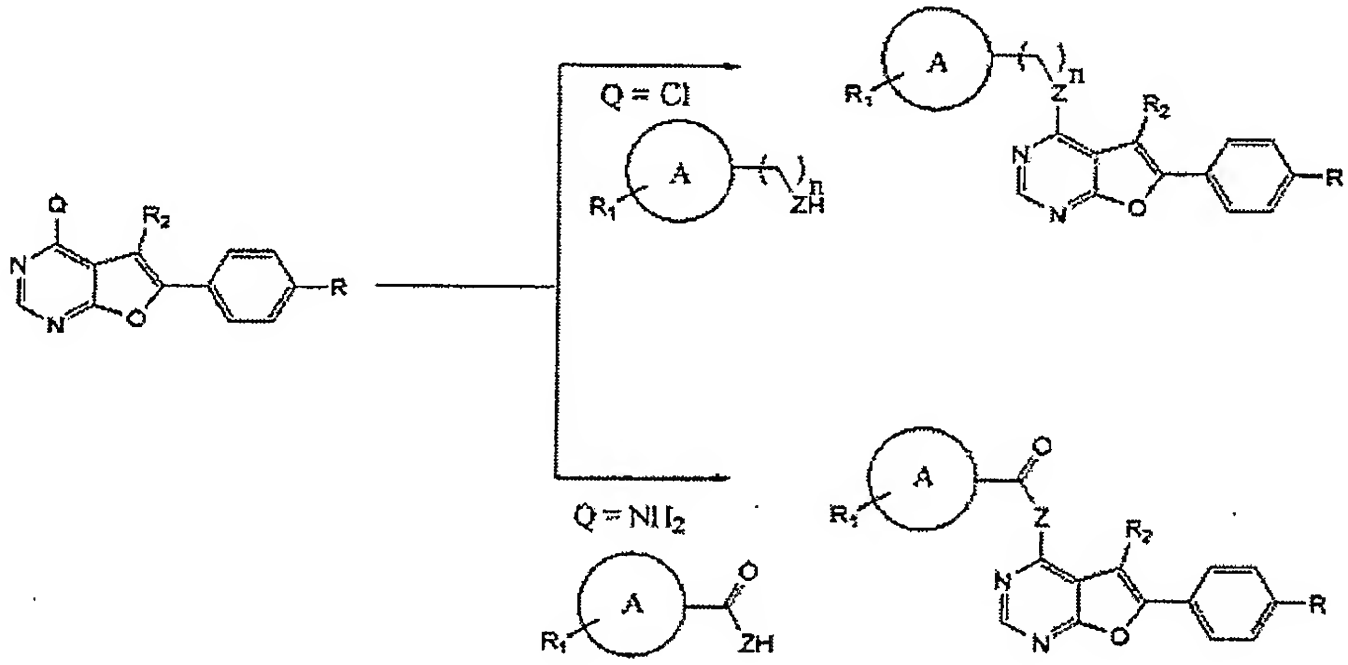
[Table 5]

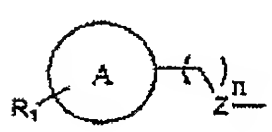
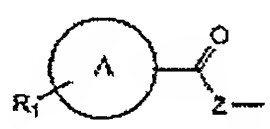
	R'	R_2	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)	Yield (%)
VIIa	Cl	H	8.85 (s, 1H), 8.07 (d, J = 8.4 Hz, 2H), 7.84 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H)	32
VIIb	OCH_3	H	8.78 (s, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.58 (s, 1H), 7.12 (d, J = 8.4 Hz, 2H), 3.85 (s, 3H)	18
VIIc	CH_3	H	8.80 (s, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.68 (s, 1H), 7.38 (d, J = 8.4 Hz, 2H), 2.39 (s, 3H)	27
VIId	Cl	CH_3	8.82 (s, 1H), 7.86 (d, J = 8 Hz, 2H), 7.67 (d, J = 8 Hz, 2H), 2.60 (s, 3H)	82
VIIe	OCH_3	CH_3	8.77 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 3.85 (s, 3H), 2.58 (s, 3H)	35
VIIf	CH_3	CH_3	8.78 (s, 1H), 7.71 (d, J = 8 Hz, 2H), 7.40 (d, J = 8 Hz, 2H), 2.58 (s, 3H), 2.40 (s, 3H)	15
VIIg	F	CH_3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.81~7.78 (m, 2H), 7.27~7.21 (m, 2H), 2.65 (s, 3H)	54
VIIh	I	CH_3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.87 (d, J = 8.4 Hz, 2H), 2.65 (s, 3H)	10
VIIi	Br	CH_3	8.79 (s, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.8 Hz, 2H), 2.56 (s, 3H)	43
VIIj	OPh	CH_3	8.79 (s, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.8 Hz, 1H), 7.52~7.42 (m, 1H), 7.28~7.06 (m, 5H), 2.59 (s, 3H)	7
VIIk	SCH_3	CH_3	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 2.66 (s, 3H), 2.55 (s, 3H)	20
VIIl	Cl	Et	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H), 3.05 (q, J = 7.6 Hz, 2H), 1.32 (t, J = 7.6 Hz, 3H)	47
VIIm	Cl	$CH(CH_3)_2$	8.85 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 3.54~3.42 (m, 1H), 1.42 (d, J = 7.2 Hz, 6H)	33
VIIo	Cl		8.87 (s, 1H), 7.51 (m, 4H), 7.39 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H)	28
VIIr	H		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.67~7.64 (m, 3H), 7.44~7.27 (m, 3H), 6.65-6.60 (m, 2H)	23
VIIs	NO_2	CO_2Et	8.99 (s, 1H), 8.44 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 8.8 Hz, 2H), 4.44 (q, J = 3.2 Hz, 2H), 1.32 (t, J = 3.2 Hz, 3H)	2
VIIu	Cl		8.88(s, 1H), 7.56~7.47 (m, 9H)	40
VIIv	Cl		8.90 (s, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.67~7.64 (m, 6H)	43
VIIw	OCH_3		8.80 (s, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 3.77 (s, 3H)	42
VIIx	OCH_3		8.83 (s, 1H), 7.38~7.58 (m, 7H), 6.97 (d, J = 8.8 Hz, 2H), 3.78 (s, 3H)	62
VIIy	OCH_3		8.23 (s, 1H), 7.52~7.46 (m, 4H), 6.85 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H)	34

Example 8: Preparation of 4,5,6-substituted furopyrimidine-based compound

A compound furopyrimidine-based compound of the present invention was prepared by using the compound VI or VII obtained in Example 6 or 7 as a starting material.

[Reaction Formula 7]



 and  are expressed as "C" , respectively.

(1) Preparation of 4-anilino-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (5)

2 ml of n-butylalcohol (or ethylalcohol or isofuropylalcohol) was added dropwisely to 79.5mg (0.3 mmol) of 4-chloro-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (VIIa) and 55.9 mg (0.6 mmol) of anilin and heated and refluxed for four hours, from which the solvent was then removed. The resultant mixture was dissolved in 1 ml of dimethylsulfoxide, filtered by applying it to 15 ml of water, sufficiently washed with water and n-hexane, and then dried to obtain an off-white solid product of 4-anilino-6-(4-

chlorophenyl)furo[2,3,d]pyrimidine (5). Compounds 6 to 64, 85, 89, 91 to 93, 107 to 111, 118 to 122, 127 and 132 of table 6 were each obtained using the same method.

(2) Preparation of 4-(4-methoxybenzoylamino)-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (66)

1 ml of pyrimidine and 511.8 mg (3 mmol) of 4-methoxybezoyl chloride were applied to 245.66 mg (1 mmol) of the 4-amino-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (VIa) prepared in the Example 6, heated and refluxed for two hours, from which pyridine was then removed by decompression. 1 N of sodium hydroxide aqueous solution was applied to the resultant mixture, and an organic layer was extracted with ethylacetate twice or three times. The obtained organic layer was washed with salt water, dried, condensed, and then, purified by column chromatography to obtain a brown solid product of 4-(4-methoxybenzoylamino)-t-(4-chlorophenyl)furo[2,3,d]pyrimidine (66). Compounds 65 and 67 to 73 of Table 6 were also each obtained using the same method.

(3) Preparation of 4-(3-methoxyphenoxy)-5-methyl-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (74)

2 ml of tetrahydrofuran (THF) was added dropwisely to 37.2 mg (0.3 mmol) of 3-methoxypenol, to which 24 mg (0.6 mmol) of sodium hydride (60% NaH) and then was stirred for about 10 minutes at a room temperature. 0.3 mmol of the 4-chloro-5-methyl-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (VIId) prepared in Example 7 was added to the reaction solution, then was stirred during two hours at the room temperature and was cooled before slowly adding 10 ml of water dropwisely. The generated solid was filtered, washed and dried with sufficient

water and n-hexane to obtain a brown solid product of 4-(3-methoxyphenoxy)-5-methyl-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (74). Compounds 75 to 78 and 126 of Table 6 were also each obtained using the same method.

(4) Preparation of 4-(3-hydroxyanilino)-5,6-di(4-hydroxyphenyl)furo{2,3,d]pyrimidine (90)

A mixture of 150 mg (0.31 mmol) of the 4-(3-hydroxyanilino)-5,6-di(4-methoxyphenyl)furo[2,3,d]pyrimidine (89) prepared in the above Example and 752 mg (6.51 mmol) of pyridine chloride were heated and refluxed at 210°C for three hours. Waster was applied to the reactant, from which an organic layer was extracted with ethylacetate twice or three times. The obtained organic layer was dried, condensed and then purified by column chromatography to obtain 15 mg of a brown solid product of 4-(3-hydroxyanlyrino)-5,6-di(4-hydroxyphenyl)furo[2,3,d]pyrimidine (90).

(5) Preparation of 4-(2-pyridilamino)-5-methyl-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (96)

A mixture obtained by dissolving 265.1 mg (1 mmol) of the 4-chloro-5-methyl-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (VIId) prepared in Example 7 and 141.17 mg (1.5 mmol) of 2-aminopyridine in 3 ml of dimethylformamide was cooled at 0°C, into which 80 ml (2 mmol) of sodium hydride (60% NaH) was added and then stirred at a room temperature for three to eight hours. Saturated ammonium chloride (NH_4Cl) aqueous solution was applied to the reactant and an organic layer was extracted with ethylacetate twice or three times. The obtained organic layer was dried, condensed and then purified to obtain a brown solid

product of 4-(2-pyridilamino)-5-methyl-t-(4-chlorophenyl)furo[2,3,d]pyrimidine (96). Compounds 94, 95, 97-106, 116 and 117, 123, 125, and 129 to 131 of Table 6 were each obtained using the same method.

(6) Preparation of 4-(trans-4-hydroxycyclohexylamino)-5-menyl-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (113)

2.2 mmol of triethylamine (Et_3NH) was added to a mixture obtained by dissolving 265.1 mg (1 mmol) of the 4-chloro-5-methyl-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (VIId) prepared in Example 7 and 303.3 mg (2 mmol) of trans-4-aminocyclohexanol chloride in 3 ml of n-butylalcohol, which was heated and refluxed, and then, stirred for 3 to 12 hours. A saturated ammonium chloride (NH_4Cl) aqueous solution was applied to the reactant and an organic layer was extracted with ethylacetate twice or three times. The obtained organic layer was dried and condensed, and then, purified by column chromatography to obtain 4-(trans-4-hycroxycyclohexylamino)-5-methyl-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (113). Compounds 112, 114 and 115 of Table 6 were also each obtained using the same method.

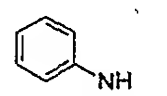
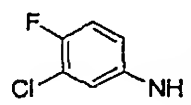
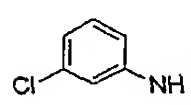
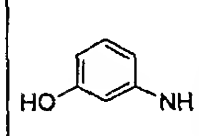
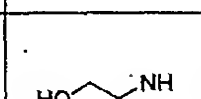
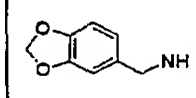
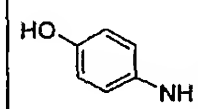
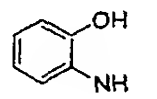
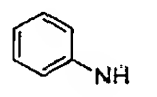
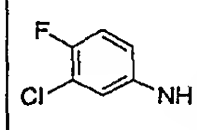
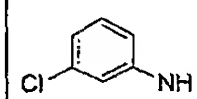
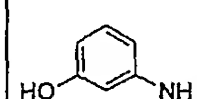
(7) Preparation of 4-(3-hydroxyphenoxy)-5-methyl-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (79)

5 ml of dichloromethane (CH_2Cl_2) was applied to 366.86 mg (1 mmol) of 4-(3-methoxyphenoxy)-5-methyl-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (74) prepared in the above Example and cooled at -78°C, to which 0.25 ml of BBr_3 (1M in dichloromethane) was slowly applied dropwisely. The resultant mixture was stirred at a room temperature for 12 hours, to which saturated sodium

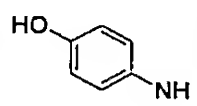
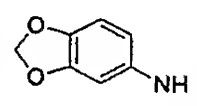
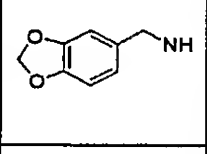
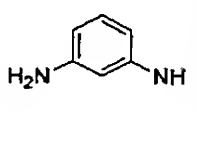
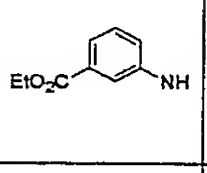
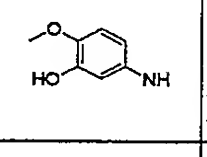
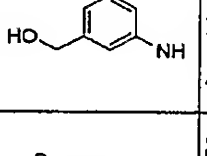
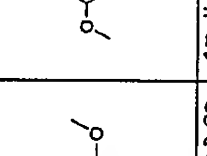
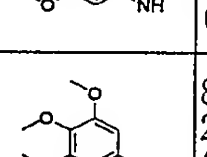
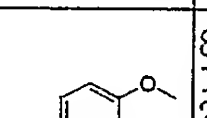
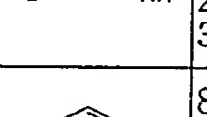
hydroxy carbon (Na_2HCO_3) aqueous solution was slowly applied and an organic layer was extracted with ethylacetate twice or three times. The obtained organic layer was washed with salt water, dried, condensed, and then, purified by column chromatography to obtain 4-(3-hydroxyphenoxy)-5-methyl-6-(4-chlorophenyl)furo[2,3,d] pyrimidine (79). Compounds 80 to 84, 86, 87, 124 and 128 were also obtained, respectively, by using the compounds 19, 69, 27, 25, 22, 59, 62, 123 and 127 of Table 6 according to the same method.

Table 6-1 to 6-10 show analysis results of the thusly-obtained 4,5,6-substituted furopyrimidine-based compounds.

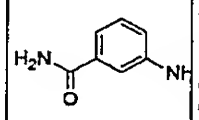
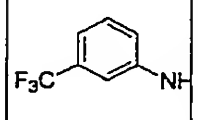
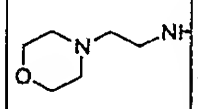
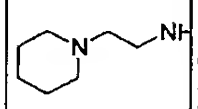
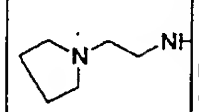
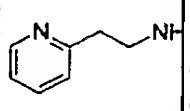
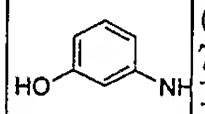
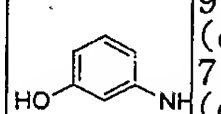
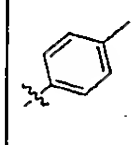
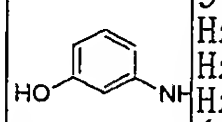
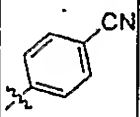
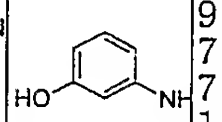
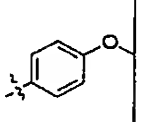
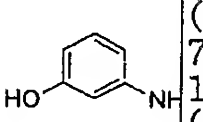
[Table 6-1]

	R	R_2	C	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)	mp (℃)	Yield (%)
5	Cl	H		9.9 (s, 1H), 8.45 (s, 1H), 7.89~7.79 (m, 4H), 7.54~7.63 (m, 3H), 7.40 (t, J = 8 Hz, 2H), 7.11 (t, J = 6.8 Hz, 1H)	255~256	39
6	Cl	H		10.02 (s, 1H), 8.48 (s, 1H), 8.21 (dd, J = 8.8, 2.4 Hz, 1H), 7.83 (d, J = 8.8 Hz, 2H), 7.74~7.68 (m, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.53 (s, 1H), 7.44 (d, J = 8.8 Hz, 1H)	239~241	90
7	Cl	H		10.03 (s, 1H), 8.51 (s, 1H), 8.13 (d, J = 2 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 1H), 7.60 (br d, 3H), 7.42 (t, J = 8 Hz, 1H), 7.14 (dd, J = 8, 2 Hz, 1H)	259~260	81
8	Cl	H		9.76 (s, 1H), 9.54~9.36 (br s, 1H), 8.42 (s, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.58 (s, 1H), 7.37 (d, J = 2.4 Hz, 1H), 7.20 (d, J = 8 Hz, 1H), 7.13 (t, J = 8 Hz, 1H), 6.49 (dd, J = 8, 2.4 Hz, 1H)	277~278	77
9	Cl	H		8.26 (s, 1H), 8.18~8.02 (br s, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.45 (s, 1H), 4.90~4.78 (m, 1H), 3.72~3.48 (m, 4H)	223~224	60
10	Cl	H		8.48 (t, J = 5.6 Hz; 1H), 8.28 (s, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.43 (s, 1H), 6.94 (s, 1H), 6.86 (s, 2H), 5.98 (s, 2H), 4.64 (d, J = 5.6 Hz, 2H)	200~201	26
11	Cl	H		9.68 (s, 1H), 9.34 (s, 1H), 8.34 (s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.40 br s, 1H), 6.79 (d, J = 8.8 Hz, 2H)	284~285	50
12	Cl	H		9.84 (s, 1H), 9.27 (s, 1H), 8.32 (s, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.60 (t, 3H), 7.42~7.28 (br s, 1H), 7.10 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 8 Hz, 1H), 6.87 (t, J = 7.6 Hz, 1H)	244~245	44
13	Cl	CH_3		8.70 (s, 1H), 8.37 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.38 (t, 2H), 7.13 (t, 1H), 2.65 (s, 3H)	160~161	32
14	Cl	CH_3		8.78 (s, 1H), 8.41 (s, 1H), 7.94 (dd, J = 6.8, 2.4 Hz, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.71~7.65 (m, 1H), 7.62 (d, J = 8.8 Hz, 2H), 7.43 (t, J = 9.2 Hz, 1H), 2.65 (s, 3H)	179~180	16
15	Cl	CH_3		8.79 (s, 1H), 8.45 (s, 1H), 7.86 (s, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.40 (t, J = 8 Hz, 1H), 7.15 (t, J = 8 Hz, 1H), 2.66 (s, 3H)	151~152	78
16	Cl	CH_3		9.42 (s, 1H), 8.57 (s, 1H), 8.38 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.22~6.98 (m, 3H), 6.52 (dd, J = 8, 1.2 Hz, 1H), 2.62 (s, 3H)	130~132	50

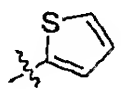
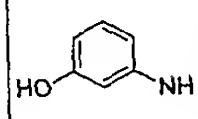
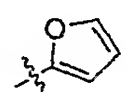
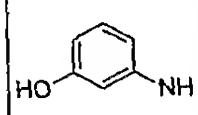
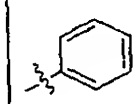
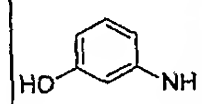
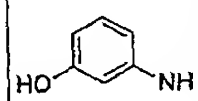
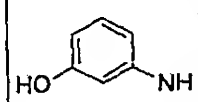
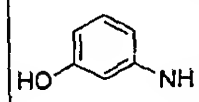
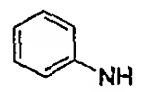
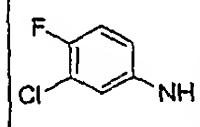
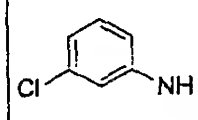
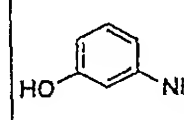
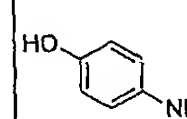
[Table 6-2]

	R	R_2	C	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)	mp (℃)	Yield (%)
17	Cl	CH_3		9.34 (s, 1H), 8.51 (s, 1H), 8.26 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8 Hz, 2H), 6.77 (d, J = 8 Hz, 2H), 2.61 (s, 3H)	273~275	62
18	Cl	CH_3		8.60 (s, 1H), 8.32 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 2.4 Hz, 1H), 7.02 (dd, J = 8, 2.4 Hz, 1H),7.25 (d, J = 8 Hz, 1H), 6.04 (s, 2H), 2.63 (s, 3H)	196~197	83
19	Cl	CH_3		8.25 (s, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 6 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 6.96 (s, 1H), 6.85 (s, 2H), 5.97 (s, 2H), 4.65 (d, J = 6 Hz, 2H), 2.58 (s, 3H)	164~165	83
20	Cl	CH_3		8.50~8.42 (br s, 1H), 8.35 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 6.99 (t, J = 8 Hz, 1H), 6.92~6.84 (br s, 1H), 6.76 (dd, J = 8, 0.8 Hz, 1H), 6.34 (dd, J = 8, 1.2 Hz, 1H), 5.18~5.04 (br s, 2H), 2.60 (s, 3H)	185~186	45
21	Cl	CH_3		8.93 (s, 1H), 8.41 (s, 1H), 8.25 (s, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 8.8 Hz, 2H), , 7.52 (t, J = 8 Hz, 1H), 4.34 (q, J = 7.2 Hz, 2H), 2.67 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H)	161~162	78
22	Cl	CH_3		9.07 (s, 1H), 8.49 (s, 1H), 8.30 (s, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.10 (s, 1H), 6.96 (d, J = 8.8 Hz, 1H), , 6.91 (d, J = 8.8 Hz, 1H), 3.77 (s, 3H), 2.61 (s, 3H)	219~220	38
23	Cl	CH_3		8.70 (s, 1H), 8.37 (s, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.63~7.48 (m, 4H), 7.32 (t, J = 8 Hz, 1H), 7.07 (d, J = 8 Hz, 1H), 5.25 (t, J = 5.6 Hz, 1H), 4.52 (d, J = 5.6 Hz, 2H), 2.64 (s, 3H)	196~197	63
24	Cl	CH_3		8.24 (s, 1H), 7.75 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 5.6 Hz, 1H), 7.59 (d, J = 8.8 Hz, 2H), 6.52 (d, J = 2 Hz, 2H), 6.36 (d, J = 2 Hz, 1H), 4.68 (d, J = 5.6 Hz, 2H), 3.75 (s, 6H), 2.60 (s, 3H)	208~209	28
25	Cl	CH_3		8.58 (s, 1H), 8.42 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 2.4 Hz, 2H), 6.28 (t, J = 2.4 Hz, 1H), 3.76 (s, 6H), 2.64 (s, 3H)	164~165	54
26	Cl	CH_3		8.58 (s, 1H), 8.38 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.05 (s, 2H), 3.78 (s, 6H), 3.66 (s, 3H), 2.65 (s, 3H)	219~220	75
27	Cl	CH_3		8.46 (s, 1H), 8.26 (s, 1H), 8.07 (d, J = 2.8 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.8 Hz, 1H), 6.67 (dd, J = 8.8, 2.8 Hz, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 2.65 (s, 3H)	214~215	64
28	Cl	CH_3		8.92 (s, 1H), 8.46 (s, 1H), 8.19 (s, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.68~7.52 (m, 4H), 2.67 (s, 3H)	269~270	54

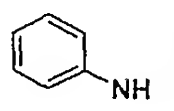
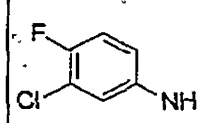
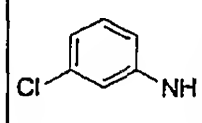
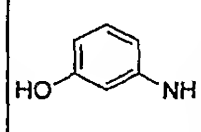
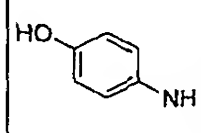
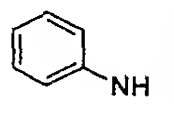
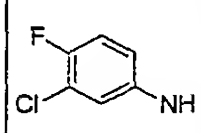
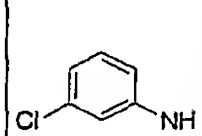
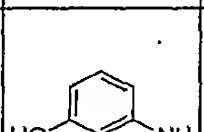
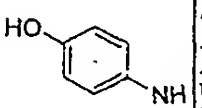
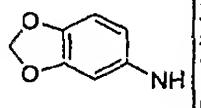
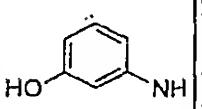
[Table 6-3]

	R	R_1	C	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)	mp (℃)	Yield (%)
29	Cl	CH_3		8.86 (s, 1H), 8.40 (s, 1H), 8.20 (s, 1H), 7.99 (s, 1H), 7.87 (d, J = 8 Hz, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 3H), 7.48~7.38 (m, 2H), 2.68 (s, 3H)	221~222	33
30	Cl	CH_3		8.92 (s, 1H), 8.44 (s, 1H), 8.10 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.58 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 2.67 (s, 3H)	151~152	64
31	Cl	CH_3		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 6.32~6.18 (br s, 1H), 3.84~3.60 (m, 6H), 2.71 (t, J = 5.6 Hz, 2H), 2.59 (s, 7H),	165~166	68
32	Cl	CH_3		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.8 Hz, 2H), 6.58~6.40 (br s, 1H), 3.61 (dd, J = 10.4, 6 Hz, 2H), 2.63 (t, J = 6 Hz, 2H), 2.58 (s, 3H), 2.56~2.32 (br s, 4H), 1.70~1.38 (m, 6H)	155~156	50
33	Cl	CH_3		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 6.28 (m, 1H), 3.65 (dd, J = 10.8, 6 Hz, 2H), 2.80 (t, J = 6 Hz, 2H), 2.66~2.54 (m, 4H), 2.53 (s, 3H), 1.88~1.74 (m, 4H)	163~164	82
34	Cl	CH_3		8.55 (d, J = 4.4 Hz, 1H), 8.37 (s, 1H), 7.70~7.60 (m, 3H), 7.43 (d, J = 8.4 Hz, 2H), 7.26~7.16 (m, 3H), 4.01 (dd, J = 10, 6.4 Hz, 2H), 3.16 (t, J = 6.4 Hz, 2H), 2.61 (s, 3H)	164~165	71
35	Cl	CH_2CH_3		9.44 (s, 1H), 8.39 (d, J = 5.6 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 7.17~7.12 (m, 2H), 7.05 (dd, J = 8.0, 1.2 Hz, 1H), 6.54 (dd, J = 8.0, 2.4 Hz, 1H), 3.11 (q, J = 7.4 Hz, 2H), 1.26(t, J = 7.4 Hz, 3H)	215~216	11
36	Cl	$CH(CH_3)_2$		9.49 (s, 1H), 8.45 (s, 1H), 7.80 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.18 (s, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.54 (d, J = 7.6 Hz, 1H), 3.64~3.50 (m, 1H), 1.30 (d, J = 6.8 Hz, 6H)	227~228	21
37	Cl			9.53 (s, 1H), 8.53 (s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.52~7.46 (m, 6H), 7.08 (t, J = 8.0 Hz, 1H), 6.74(s, 1H), 6.62 (dd, J = 8.0, 1.2 Hz, 1H), 6.45 (dd, J = 8.0 2.4 Hz, 1H), 2.48 (s, 3H)	250~251	33
38	Cl			9.50 (s, 1H), 8.53 (s, 1H), 7.72~7.65 (m, 4H), 7.52~7.45 (m, 4H), 7.08 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 7.6 Hz, 2H), 6.73 (dd, J = 8.0, 1.2 Hz, 1H), 6.47 (dd, J = 8.0, 2.4, 1H)	255~256	9
39	H			9.54(s, 1H), 8.52 (s, 1H), 7.67 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.0, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.4 Hz, 1H), 7.08 (t, J = 8.0, 1H), 7.05 (s, 2H), 6.76 (s, 1H), 6.67 (dd, J = 8.0, 1.2 Hz, 1H), 6.45 (dd, J = 8.0 2.4 Hz, 1H), 3.90 (s, 3H)	192~193	12

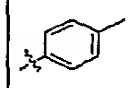
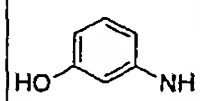
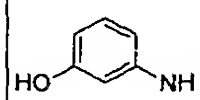
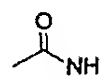
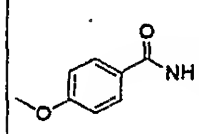
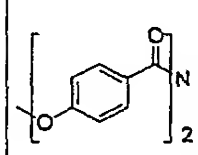
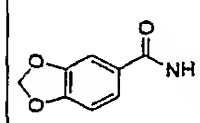
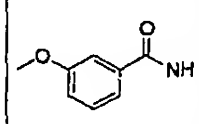
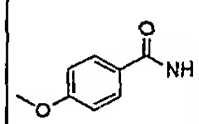
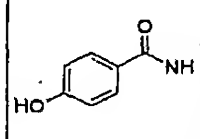
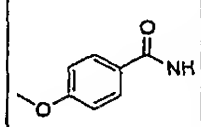
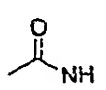
[Table 6-4]

	R	R_2	C	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)	mp (℃)	Yield (%)
40	H			9.53(s, 1H), 8.53 (s, 1H), 7.98 (d, J = 5.2 Hz 1H), 7.70 (s, 1H), 7.62~7.59 (m, 3H), 7.47~7.42 (m, 3H), 7.11~7.07 (m, 2H), 6.92 (s, 1H), 6.72 (dd, J = 8.0, 1.2 Hz, 1H), 6.45 (dd, J = 8.0, 2.4 Hz, 1H)	234~235	11
41	H			9.53 (s, 1H), 8.53 (s, 1H), 8.09 (dd, J = 2.0, 0.8 Hz, 1H), 7.65 (s, 1H), 7.62~7.59 (m, 2H), 7.53~7.46 (m, 3H), 7.31 (t, J = 2.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 6.97 (dd, J = 8.0, 1.2 Hz, 1H), 6.87 (dd, J = 3.2, 0.8 Hz, 1H), 6.80 (dd, J = 3.2, 2.0 Hz, 1H), 6.50 (dd, J = 8.0, 2.4 Hz, 1H)	210~211	67
42	H			9.52 (s, 1H), 8.54 (s, 1H), 7.69 (s, 4H), 7.53~7.51 (m, 2H), 7.45~7.37 (m, 4H), 7.06 (t, J = 8.0 Hz, 1H), 7.03 (s, 1H), 6.66 (s, 1H), 6.60 (dd, J = 8.0, 1.2 Hz, 1H), 6.44 (dd, J = 8.0, 2.4 Hz, 1H)	221~222	80
43	I	CH_3		9.43 (s, 1H), 8.57 (s, 1H), 8.38 (s, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.17 (s, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.05 (dd, J = 8.0, 1.2 Hz, 1H), 6.52 (dd, J = 8.0, 2.4 Hz, 1H), 2.62 (s, 3H)	249~250	10
44	F	CH_3		9.43 (s, 1H), 8.53 (s, 1H), 8.37 (s, 1H), 7.77 (m, 2H), 7.37 (m, 2H), 7.19 (s, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.05 (dd, J = 8.0, 1.2 Hz, 1H), 6.52 (dd, J = 8.0, 2.4 Hz, 1H), 2.60 (s, 3H)	229~230	54
45	Br	CH_3		9.43 (s, 1H), 8.58 (s, 1H), 8.39 (s, 1H), 7.75 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.8 Hz, 2H), 7.24~7.02 (m, 3H), 6.53 (dd, J = 8.0, 2.0 Hz, 1H), 2.62 (s, 3H)	220~221	59
46	CH_3	H		9.83 (s, 1H), 8.43 (s, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.49 (s, 1H), 7.44~7.26 (m, 4H), 7.10 (t, J = 7.2 Hz, 1H), 2.38 (s, 3H)	187~188	43
47	CH_3	H		9.98 (s, 1H), 8.47 (s, 1H), 8.22 (d, J = 6.8 Hz, 1H), 7.76~7.66 (m, 3H), 7.48~7.30 (m, 4H), 2.37 (s, 3H)	249~251	28
48	CH_3	H		9.98 (s, 1H), 8.50 (s, 1H), 8.15 (s, 1H), 7.82~7.68 (m, 3H), 7.51 (s, 1H), 7.45~7.32 (m, 3H), 7.13 (dd, J = 8.0, 2.0 Hz, 1H), 2.38 (s, 3H)	245~247	31
49	CH_3	H		9.69 (s, 1H), 9.46 (s, 1H), 8.42 (s, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.50 (s, 1H), 7.41 (s, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H), 6.50 (dd, J = 8.0, 2.0 Hz, 1H), 2.37 (s, 3H)	277~279	54
50	CH_3	H		9.60 (s, 1H), 9.32 (s, 1H), 8.32 (s, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.0 Hz, 3H), 6.79 (d, J = 8.8 Hz, 2H), 2.36 (s, 3H)	285~286	56

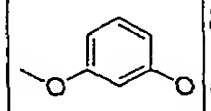
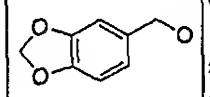
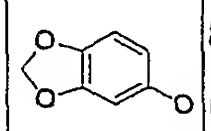
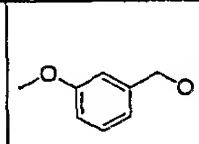
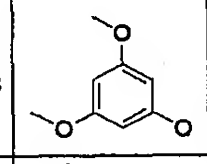
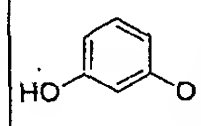
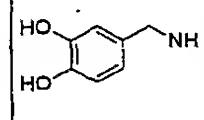
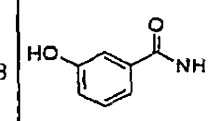
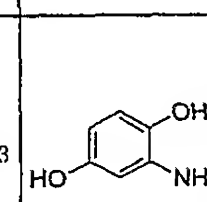
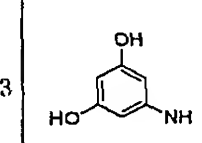
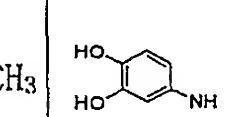
[Table 6-5]

	R	R_2	C	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)	mp (℃)	Yield (%)
51	CH_3	CH_3		8.64 (s, 1H), 8.35 (s, 1H), 7.72~7.58 (m, 4H), 7.42~7.28 (m, 4H), 7.11 (t, J = 7.6 Hz, 1H), 2.63 (s, 3H), 2.39 (s, 3H)	165~167	85
52	CH_3	CH_3		8.74 (s, 1H), 8.40 (s, 1H), 7.95 (dd, J = 6.8, 2.4 Hz, 1H), 7.73~7.61 (m, 3H), 7.43 (t, J = 8.8 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 2.64 (s, 3H), 2.39 (s, 3H)	175~177	75
53	CH_3	CH_3		8.75 (s, 1H), 8.43 (s, 1H), 7.86 (s, 1H), 7.68~7.54 (m, 3H), 7.44~7.26 (m, 3H), 7.15 (d, J = 8.4 Hz, 1H), 2.64 (s, 3H), 2.39 (s, 3H)	150~151	59
54	CH_3	CH_3		9.41 (s, 1H), 8.51 (s, 1H), 8.36 (s, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.22~6.97 (m, 3H), 6.51 (d, J = 8.0 Hz, 1H), 2.61 (s, 3H), 2.38 (s, 3H)	200~201	67
55	CH_3	CH_3		9.32 (s, 1H), 8.45 (s, 1H), 8.24 (s, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.35 (br d, 4H), 6.77 (d, J = 8.0 Hz, 2H), 2.59 (s, 3H), 2.38 (s, 3H)	267~268	74
56	OCH_3	H		9.80 (s, 1H), 8.41 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.42~7.32 (m, 3H), 7.14~7.06 (m, 3H), 3.83 (s, 3H)	228~230	16
57	OCH_3	H		9.95 (s, 1H), 8.46 (s, 1H), 8.23 (dd, J = 6.8, 2.4 Hz, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.78~7.68 (m, 1H), 7.44 (t, J = 9.2 Hz, 1H), 7.37 (s, 1H), 7.11 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H)	208~209	4
58	OCH_3	H		9.95 (s, 1H), 8.48 (s, 1H), 8.15 (t, J = 2.4 Hz, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.77~7.70 (m, 1H), 7.45~7.28 (m, 2H), 7.14~7.08 (m, 3H), 3.88 (s, 3H)	216~218	10
59	OCH_3	H		9.66 (s, 1H), 9.45 (s, 1H), 8.41 (s, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.41 (s, 1H), 7.30~6.98 (m, 5H), 6.49 (dd, J = 8.0, 1.2 Hz, 1H), 3.83 (s, 3H)	257~258	31
60	OCH_3	H		9.57 (s, 1H), 9.31 (s, 1H), 8.30 (s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.16 (br s, 1H), 7.09 (d, J = 8.0 Hz, 2H), 6.79 (d, J = 8.0 Hz, 2H), 3.83 (s, 3H)	268~269	70
61	OCH_3	H		9.69 (s, 1H), 8.36 (s, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.51 (s, 1H), 7.30 (s, 1H), 7.20~7.00 (m, 3H), 6.94 (d, J = 8.4 Hz, 1H), 6.03 (s, 2H), 3.83 (s, 3H)	220~222	28
62	OCH_3	CH_3		9.42 (s, 1H), 8.50 (s, 1H), 8.36 (s, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.22~7.00 (m, 5H), 6.51 (dd, J = 8.0, 2.4 Hz, 1H), 3.84 (s, 3H), 2.59 (s, 3H)	227~228	40

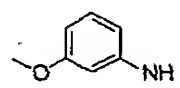
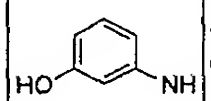
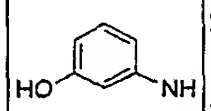
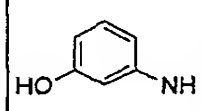
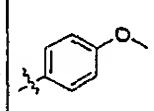
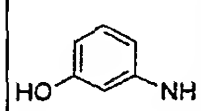
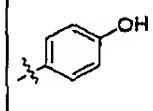
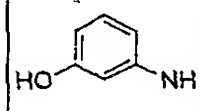
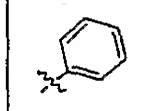
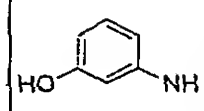
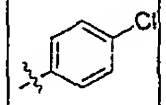
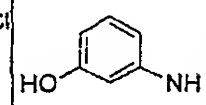
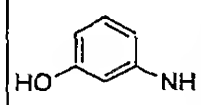
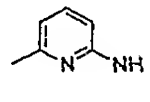
[Table 6-6]

	R	R_2	C	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)	mp (℃)	Yield (%)
63	OCH_3			9.53 (s, 1H), 8.50 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.05 (m, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.69 (s, 1H), 6.44 (dd, *J* = 8.0, 2.4 Hz, 1H), 3.76 (s, 3H), 2.48 (s, 3H)	220~221	15
64	OPh	CH_3		9.43 (s, 1H), 8.53 (s, 1H), 8.37 (s, 1H), 7.82~7.70 (m, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.24~6.98 (m, 8H),6.52 (d, *J* = 8.0 Hz, 1H), 2.61 (s, 3H)	231~232	16
65	Cl	H		11.20 (s, 1H), 8.67 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.58 (s, 1H), 2.24 (s, 3H)	235~236	7
66	Cl	H		11.45 (s, 1H), 8.76 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 2H), 8.00 (d, *J* = 8 Hz, 2H), 7.60 (d, *J* = 8 Hz, 1H), 7.51 (s, H), 7.14 (d, *J* = 8.4 Hz, 2H), 3.87 (s, 3H)	159~160	7
67	Cl	CH_3		8.73 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 4H), 7.32 (s, 2H), 7.26~7.17 (m, 2H), 3.75 (s, 6H), 2.42 (s, 3H)	182~183	12
68	Cl	CH_3		11.06~11.18 (br s, 1H), 8.80 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.71 (dd, *J* = 8, 1.2 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 1.2 Hz, 1H), 7.10 (d, *J* = 8 Hz, 1H), 6.17 (s, 2H), 2.31 (s, 3H)	237~239	7
69	Cl	CH_3		11.44~11.26 (br s, 1H), 8.83 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.72~7.54 (m, 4H), 7.50 (t, *J* = 8.4 Hz, 1H), 7.24 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.86 (s, 3H), 2.33 (s, 3H)	198~199	23
70	Cl	CH_2CH_3		11.20 (s, 1H), 8.85 (s, 1H), 8.05 (d, *J* = 7.6 Hz, 2H), 7.78 (d, *J* = 7.2 Hz, 2H), 7.63 (d, *J* = 7.2 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 3.86 (s, 3H), 2.72 (q, *J* = 7.2 Hz, 2H), 1.11(t, *J* = 7.2 Hz, 3H)	246~247	64
71	Cl	CH_2CH_3		11.09 (s, 1H), 10.34 (s, 1H), 8.84 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 7.2 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 2.72 (q, *J* = 7.6 Hz, 2H), 1.12(t, *J* = 7.6 Hz, 3H)	209~210	37
72	F	CH_3		11.19 (s, 1H), 8.80 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 2H), 7.87~7.84 (m, 2H), 7.44~7.40 (m, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 3.87 (s, 3H), 2.28 (s, 3H)	210~211	11
73	OCH_3	H		11.12 (s, 1H), 8.62 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.35 (s, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 2.24 (s, 3H)	247~249	19

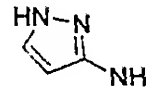
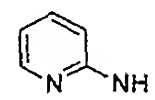
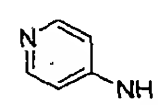
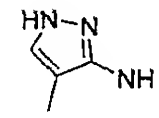
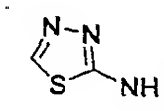
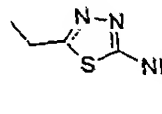
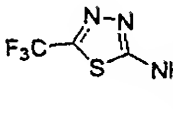
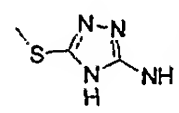
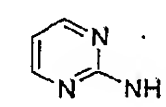
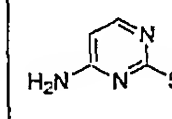
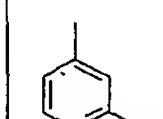
[Table 6-7]

	R	R_2	C	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)	mp (℃)	Yield (%)
74	Cl	CH_3		8.49 (s, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.39 (t, J = 8 Hz, 1H), 6.96~6.86 (m, 3H), 3.78 (s, 3H), 2.62 (s, 3H)	164~166	49
75	Cl	CH_3		8.58 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.12 (s, 1H), 7.03 (t, J = 8 Hz, 1H), 6.95 (d, J = 8 Hz, 1H), 6.05 (s, 2H), 5.50 (s, 2H), 2.50 (s, 3H)	151~153	65
76	Cl	CH_3		8.49 (s, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.06~6.95 (m, 2H), 6.82~6.75 (m, 1H), 6.10 (s, 2H), 2.62 (s, 3H)	168~170	50
77	Cl	CH_3		8.59 (s, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.34 (t, J = 8 Hz, 1H), 7.16~7.04 (m, 2H), 6.93 (dd, J = 8, 2.4 Hz, 1H), 5.60 (s, 2H), 3.78 (s, 3H), 2.55 (s, 3H)	101~102	57
78	Cl	CH_3		8.51 (s, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 6.52 (d, J = 2 Hz, 2H), 6.47 (t, J = 2 Hz, 1H), 3.80 (s, 6H), 2.62 (s, 3H)	159~160	73
79	Cl	CH_3		9.78 (s, 1H), 8.50 (s, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.26 (t, J = 8 Hz, 1H), 6.80~6.62 (m, 3H), 2.63 (s, 3H)	265~266	25
80	Cl	CH_3		8.79 (s, 1H), 8.71 (s, 1H), 8.24 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.8 Hz, 3H), 6.75 (s, 1H), 6.68~6.58 (m, 2H), 4.59 (d, J = 6 Hz, 2H), 2.57 (s, 3H)	205~206	13
81	Cl	CH_3		11.31~11.18 (br s, 1H), 9.86 (s, 1H), 8.82 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8 Hz, 1H), 7.39 (s, 1H), 7.37 (t, J = 8 Hz, 1H), 7.05 (d, J = 8 Hz, 1H), 2.32 (s, 3H)	280~281	55
82	Cl	CH_3		9.49 (s, 1H), 8.86 (s, 1H), 8.45 (s, 1H), 8.20 (s, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 8.4 Hz, 1H), 6.36 (dd, J = 8.4, 2.4 Hz, 1H), 2.65 (s, 3H)	346~347	7
83	Cl	CH_3		9.25 (s, 2H), 8.45 (s, 1H), 8.39 (s, 1H), 7.77 (d, J = 7.6 Hz, 2H), 7.61 (d, J = 7.6 Hz, 2H), 6.60 (s, 2H), 5.99 (d, J = 1.6 Hz, 1H), 2.60 (s, 3H)	349~350	7
84	Cl	CH_3		8.99 (br s, 1H), 8.81 (br s, 1H), 8.43 (s, 1H), 8.28 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 8.4, 2.4 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 2.59 (s, 3H)	347~348	8

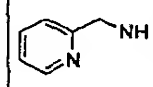
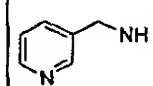
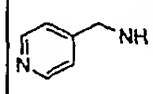
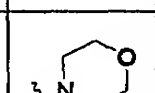
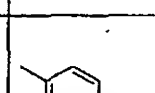
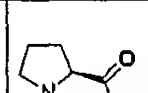
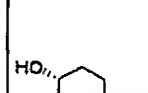
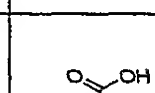
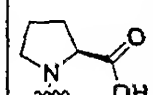
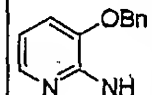
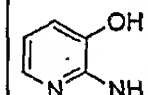
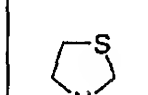
[Table 6-8]

	R	R_2	C	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)	mp (℃)	Yield (%)
85	OH	CH_3		11.92 (s, 1H), 9.57 (s, 1H), 7.80 (s, 1H), 7.25 (t, J = 8.0 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 6.88 (dd, J = 8.0, 2.4 Hz, 1H), 6.76~6.62 (m, 4H), 3.65 (s, 3H), 2.32 (s, 3H)	196~197	14
86	OH	H		10.50~9.89 (br s, 1H), 9.68~9.54 (br s, 1H), 9.52~9.36 (br s, 1H), 8.39 (s, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.40 (s, 1H), 7.33 (s, 1H), 7.25~7.08 (m, 2H), 6.92 (d, J = 8.4 Hz, 2H), 6.49 (dd, J = 8.0, 2.0 Hz, 1H)	298~300	30
87	OH	CH_3		9.92 (s, 1H), 9.40 (s, 1H), 8.47 (s, 1H), 8.34 (s, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.22~7.02 (m, 3H), 6.93 (d, J = 8.4 Hz, 2H), 6.49 (dd, J = 8.8, 2.4 Hz, 1H), 2.57 (s, 3H)	288~289	65
88	NO_2	CO_2Et		10.62 (s, 1H), 9.56 (s, 1H), 8.58 (s, 1H), 8.41~8.36 (d, J = 8.8 Hz, 2H), 8.17~8.16 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 1.2 Hz, 1H), 7.19~7.18 (m, 2H), 6.55~6.52 (m, 1H), 4.34 (q, J = 7.6 Hz, 2H), 1.16 (t, J = 7.6 Hz 3H)	209~210	37
89	OCH_3			9.52 (s, 1H), 8.48 (s, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.07 (t, 2H), 6.96 (d, J = 8.8 Hz, 2H), 6.72 (s, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.44 (dd, J = 8.0, 1.2 Hz, 1H), 3.89 (s, 3H), 3.76 (s, 3H)	187~188	63
90	OH			10.00 (s, 1H), 9.92 (s, 1H), 9.53 (s, 1H), 8.48 (s, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.12~6.96 (m, 4H), 6.77 (d, J = 8.8 Hz, 2H), 6.72 (s, 1H), 6.64 (dd, J = 8.0, 1.6 Hz, 1H), 6.43 (dd, J = 8.0, 1.6 Hz, 1H)	258~259	12
91	Cl			9.52 (s, 1H), 8.54 (s, 1H), 7.80~7.62 (br s, 5H), 7.54~7.42 (br s, 4H), 7.12~6.98 (m, 2H), 6.68 (s, 1H), 6.61 (d, J = 8.0 Hz, 1H), 6.44 (d, J = 8.0 Hz, 1H)	225~226	85
92	Cl			9.50 (s, 1H), 8.53 (s, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.08 (t, J = 8.0 Hz, 1H), 7.08~6.96 (m, 2H), 6.73 (dd, J = 8.0, 1.2 Hz, 1H), 6.46 (dd, J = 8.0, 2.4 Hz, 1H)	272~273	43
93	SCH_3	CH_3		9.44 (s, 1H), 8.53 (s, 1H), 8.37 (s, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.18 (s, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.53 (d, J = 8.0 Hz, 1H), 2.61 (s, 3H), 2.55 (s, 3H)	199~200	48
94	Cl	CH_3		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.38 (d, J = 8.0 Hz, 1H), 7.69~7.63 (m, 4H), 7.47 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.0 Hz, 1H), 2.73 (s, 3H), 2.49 (s, 3H)	189~190	66

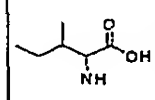
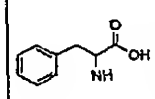
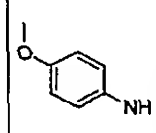
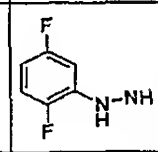
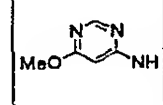
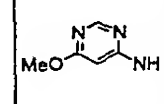
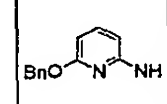
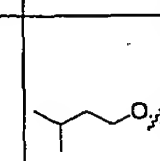
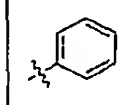
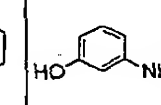
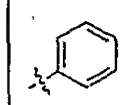
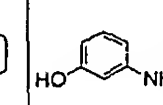
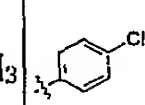
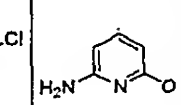
[Table 6-9]

	R	R_2	C	^{1}H NMR (400 MHz $CDCl_3$) δ (ppm)	mp (℃)	Yield (%)
95	Cl	CH_3		8.54 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.57 (s, 1H), 7.48~7.45 (m, 3H), 6.87~6.77 (br s, 1H), 6.82 (s, 1H) 2.67 (s, 3H)	218~220	41
96	Cl	CH_3		8.63 (d, J = 8.4 Hz, 1H), 8.59 (s, 1H), 8.40 (d, J = 4.8 Hz, 1H), 7.80 (s, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.06~7.00 (m, 1H), 2.73 (s, 3H)	193~195	36
97	Cl	CH_3		8.73 (s, 1H), 8.51 (s, 1H), 8.41~8.37(m, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.38~7.35 (m, 1H), 6.97 (s, 1H), 2.73 (s, 3H)	199~212	37
98	Cl	CH_3		8.61 (s, 1H), 8.56 (d, J = 6.4 Hz, 2H), 7.73 (d, J = 6.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.08 (s, 1H), 2.70 (s, 3H)	259~261	33
99	Cl	CH_3		^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23~12.13 (br s, 1H), 8.86 (s, 1H), 8.37 (s, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 2.65 (s, 3H), 2.21 (s, 3H)	241~243	22
100	Cl	CH_3		8.83 (s, 1H), 8.64 (s, 1H), 7.69 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 2.73 (s, 3H)	208~211	31
101	Cl	CH_3		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 2.88 (q, J = 7.2 Hz, 2H), 2.51 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H)	230~232	29
102	Cl	CH_3		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 2.66 (s, 3H)	257~259	36
103	Cl	CH_3		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 7.92 (s, 1H), 7.81 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 2.60 (s, 3H), 2.55 (s, 3H)	243~248	42
104	Cl	CH_3		8.79 (s, 1H), 8.64 (d, J = 4.8 Hz, 2H), 7.71 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 4.8 Hz, 1H), 2.49 (s, 3H)	199~201	68
105	Cl	CH_3		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 (s, 1H), 7.87 (d, J = 6.0 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.17~7.05 (br s, 2H), 6.25 (d, J = 6.0 Hz, 1H), 2.39 (s, 3H)	238~239	88
106	Cl	CH_3		8.59 (s, 1H), 8.45 (s, 1H), 8.16 (d, J = 4.8 Hz, 1H), 7.71 (s, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 4.8 Hz, 1H), 2.61 (s, 3H), 2.45 (s, 3H)	187~188	55

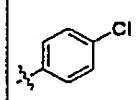
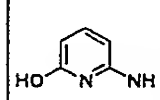
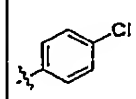
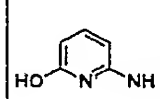
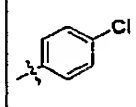
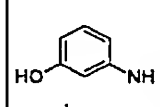
[Table 6-10]

	R	R_2	C	^{1}H NMR (400 MHz $CDCl_3$) δ (ppm)	mp (℃)	Yield (%)
107	Cl	CH_3		8.61 (d, J = 4.4 Hz, 1H), 8.40 (s, 1H), 7.72 (t, J = 8.0 Hz, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.0 Hz, 1H), 7.28~7.23 (m, 1H), 7.12 (s, 1H), 4.89 (d, J = 4.4 Hz, 2H), 2.66 (s, 3H)	184~185	89
108	Cl	CH_3		8.67 (s, 1H), 8.56 (d, J = 4.4 Hz, 1H), 8.41 (s, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.30 (dd, J = 7.6, 4.8 Hz, 1H), 5.54~5.52 (m, 1H), 4.90 (d, J = 4.4 Hz, 2H), 2.55 (s, 3H)	192~193	91
109	Cl	CH_3		8.58 (d, J = 6.4 Hz, 2H), 8.34 (s, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.44~7.27 (m, 2H), 5.62~5.48 (m, 2H), 4.91 (d, J = 6.4 Hz, 2H), 2.55 (s, 3H)	221~223	77
110	Cl	CH_3		8.47 (s, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 3.88 (t, J = 4.4 Hz, 4H), 3.64 (t, J = 4.4 Hz, 4H), 2.53 (s, 3H)	161~164	91
111	Cl	CH_3		8.56 (s, 1H), 8.49 (d, J = 8.8 Hz, 1H), 8.13 (s, 1H), 7.68 (m, 3H), 7.57 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.8 Hz, 2H), 2.71 (s, 3H), 2.33 (s, 3H)	207~211	58
112	Cl	CH_3		8.31 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 4.85 (q, J = 6.0 Hz, 1H), 3.97~3.84 (m, 2H), 3.75 (s, 3H), 2.52 (s, 3H), 2.39~2.23 (m, 2H), 2.10~2.05 (m, 2H)	98~99	81
113	Cl	CH_3		8.34 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 4.96 (d, J = 8.0 Hz, 1H), 4.23~4.11 (m, 1H), 3.79~3.69 (m, 1H), 2.51 (s, 3H), 2.25~2.18 (m, 2H), 2.10~2.05 (m, 1H), 1.57~1.54 (m, 2H), 1.40~1.33 (m, 2H)	97~99	87
114	Cl	CH_3		^{1}H NMR (400 MHz DMSO-d_6) δ 8.30 (s, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 6.50~6.40 (m, 1H), 4.82~4.90 (m, 1H), 2.58 (s, 3H), 1.98~1.82 (m, 1H), 1.60~1.39 (m, 4H), 0.96~0.92 (m, 6H)	193~200	71
115	Cl	CH_3		8.35 (s, 1H), 7.60 (d, J = 7.2 Hz, 2H), 7.45 (d, J = 7.2 Hz, 2H), 4.87 (s, 1H), 3.87~3.82 (m, 2H), 2.48 (s, 3H), 2.21~2.05 (m, 4H)	135~141	80
116	Cl	CH_3		^{1}H NMR (400 MHz $CDCl_3$) 8.71(s, 1H), 8.12 (d, J = 4.8 Hz, 1H), 8.02 (s, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.45~7.38 (m, 6H), 7.26 (t, J = 7.6 Hz, 1H), 7.00 (dd, J = 8.0, 1.2 Hz, 1H), 5.16 (s, 2H), 2.25 (s, 3H)	153~159	51
117	Cl	CH_3		^{1}H NMR (400 MHz $CDCl_3$) 8.44 (s, 1H), 7.81 (s, br, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.37~7.35 (m, 1H), 7.05 (s, br, 1H), 2.75 (s, 3H)	156~160	99
118	Cl	CH_3		^{1}H NMR (400 MHz $CDCl_3$) 8.45 (s, 1H), 7.69 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 4.85 (s, 2H), 4.08 (t, J = 6.4 Hz, 2H), 2.57 (s, 3H)	167~168	81

[Table 6-11]

	R	R_2	C	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm)	mp (℃)	Yield (%)
119	Cl	CH_3		8.29 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 6.54 (d, J = 8.0 Hz, 2H), 4.65 (t, J = 6.8 Hz, 2H), 2.60 (s. 3H), 2.12~2.10 (m, 1H), 1.60~1.55 (m, 1H), 1.36~1.30 (m, 1H), 0.99~0.91 (m, 1H)	185~192	77
120	Cl	CH_3		8.24 (s, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H). 7.26~7.14 (m, 5H), 6.97 (d, J = 6.0 Hz, 1H), 4.79~4.77 (m, 1H), 3.34~3.24 (m, 2H), 2.45 (s. 3H)	117~125	60
121	Cl	CH_3		8.43 (s, 1H), 8.29 (d, J = 2.4 Hz, 1H), 7.96~7.93 (m, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 1H), 6.76 (s, 1H), 3.96 (s, 1H), 2.67 (s, 3H)	214~216	64
122	Cl	CH_3		9.23 (s, 1H), 8.33 (s, 1H), 8.30 (s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H). 7.18~7.12 (m, 1H), 6.66~6.64 (m, 1H), 6.51~6.46 (m, 1H), 2.51 (s, 3H)	132~134	88
123	OCH_3	CH_3		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (s, 1H), 8.61 (s, 1H), 8.52 (s, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.45 (s, 1H),7.12 (d, J = 8.8 Hz, 2H), 3.92 (s, 3H), 3.84 (s, 3H), 2.55 (s. 3H)	224~227	64
124	OH	CH_3		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 9.45 (s, 1H), 8.61 (s, 1H), 8.53 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.47 (s, 1H),6.94 (d, J = 8.4 Hz, 2H), 3.92 (s, 3H), 2.54 (s, 3H)	249~253	21
125	OCH_3	CH_3		^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.16 (d, J = 8.0 Hz, 2H), 7.72~7.64 (m, 3H), 7.54 (s, 1H), 7.50~7.30 (m, 1H), 7.03 (d, J = 8.8 Hz, 2H), 6.53 (d, J = 8.0 Hz, 1H), 5.35 (s, 2H), 3.88 (s, 3H), 3.88 (s, 3H)	201~203	42
126	OCH_3	CH_3		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 4.56 (t, J = 6.4 Hz, 2H), 3.87 (s, 3H), 2.54 (s, 3H). 1.80~1.93 (m, 1H), 1.76 (q, J = 6.8 Hz, 2H), 1.01 (d, J = 6.8 Hz, 6H)	184~186	84
127	OCH_3			9.50 (s, 1H), 8.50 (s, 1H), 7.60~7.72 (br s, 5H), 7.44 (d, J = 8.8 Hz, 2H), 7.00~7.09 (m, 2H), 6.96 (d, J = 8.8 Hz, 2H), 6.62 (s, 1H), 6.59 (dd, J = 8.0, 1.2 Hz, 1H), 6.42 (dd, J = 8.0, 1.2 Hz, 1H), 3.76 (s, 3H)	264~267	67
128	OH			9.95 (s, 1H), 9.50 (s, 1H), 8.50 (s, 1H), 7.62~7.74 (br s, 5H), 7.34 (d, J = 8.8 Hz, 2H), 7.01~7.09 (m, 2H), 6.76 (d, J = 8.8 Hz, 2H), 6.57~6.65 (m, 2H), 6.42 (dd, J = 8.0, 2.0 Hz, 1H)	291~294	52
129	OCH_3			^{1}H NMR (400 MHz $CDCl_3$) .8.54 (s, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.49~7.44 (m, 3H), 7.33 (d, J = 8.8 Hz, 2H), 6.33 (d, J = 8.0 Hz, 1H), 6.27 (d, J = 8.0 Hz, 1H), 4.86 (s, br, 2H), 3.82 (s, 3H)	207~209	40

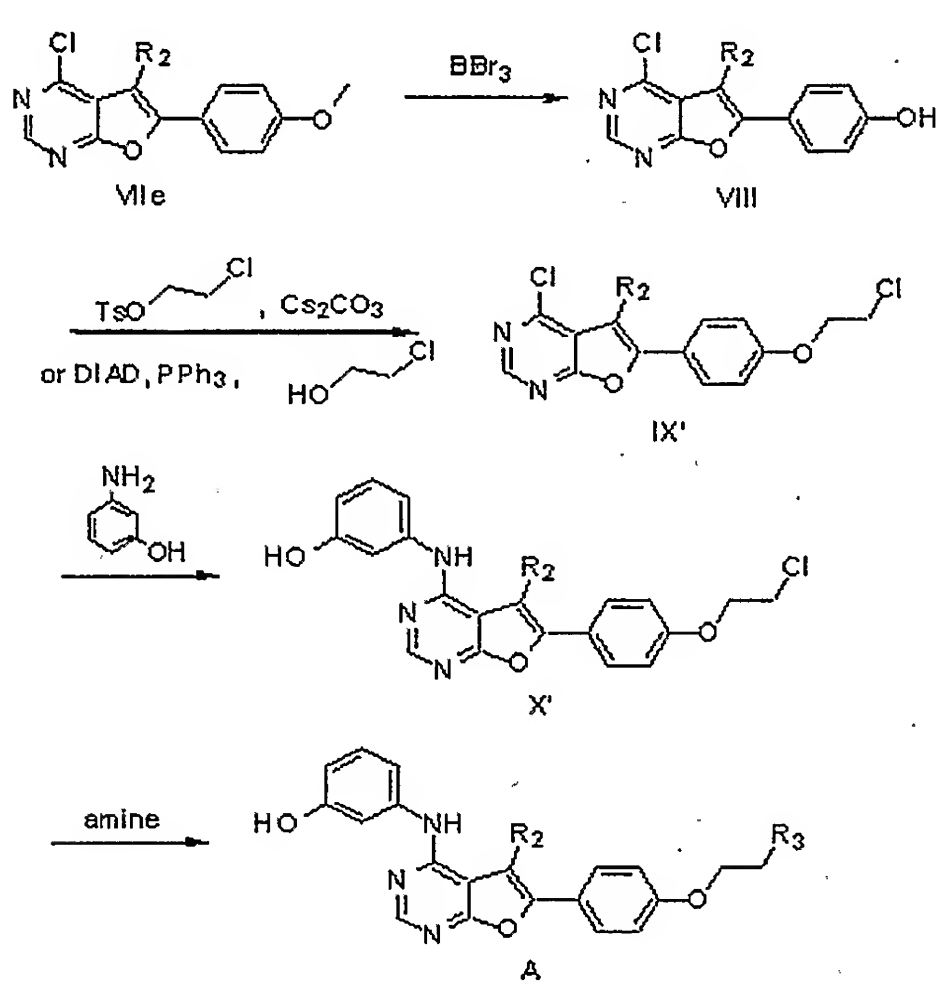
[Table 6-12]

	R	R_2	C	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm)	mp (℃)	Yield (%)
130	OCH_3			^{1}H NMR (400 MHz $CDCl_3$) 8.58 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.54~7.47 (m, 4H), 7.28~7.26 (m, 1H), 6.86 (d, J = 8.4 Hz, 2H), 6.64 (s, 1H), 6.16 (d, J = 9.2 Hz, 1H), 5.14 (d, J = 7.2 Hz, 1H), 3.83 (s, 3H)	248~249	88
131	OH			10.79 (s, 1H), 10.00 (s, 1H), 8.58 (s, 1H), 7.65~7.46 (m, 6H), 7.33~7.26 (m, 3H), 6.77 (d, J = 8.4 Hz, 2H), 6.21 (d, J = 7.6 Hz, 1H)	299~300	76
132	OCH_3			9.49 (s, 1H), 8.49 (s, 1H), 7.70~7.64 (m, 4H), 7.40 (d, J = 9.2 Hz, 2H), 7.07 (t, J = 8.0 Hz, 1H), 7.03 (s, 1H), 6.98 (d, J = 9.2 Hz, 2H), 6.90 (s, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.45 (dd, J = 8.0, 1.2 Hz, 1H), 3.77 (s, 3H)	251~253	66.4

Example 9

A compound "A", a precursor of the compounds of the present invention, can be prepared by using the thusly-obtained compound VIII, for example, by the following Reaction Formula 8:

[Reaction Formula 8]



Example 9-1: Preparation of 4-chloro-5-methyl-6-(4-hydroxyphenyl) furo[2,3,d]pyrimidine (VIII-2)

10 ml of dichloromethane was added to 1.268g (4.6 mmol) of 4-chloro-5-methyl-6-(4-methoxyphenyl)furo[2,3,d]pyrimidine (VIIe) obtained in Example 7, cooled at -78°C, to which 13.85 ml of BBr_3 (1M in dichloromethane) was slowly applied dropwisely. The resultant mixture was stirred at a room temperature for 12 hours, to which saturated sodium hydroxy carbon (Na_2HCO_3) aqueous solution was slowly applied and an organic layer was extracted with ethylacetate twice or three times. The obtained organic layer was washed with salt water, dried, condensed, and then, purified by column chromatography to obtain a yellow solid product of 4-chloro-5-methyl-6-(4-hydroxyphenyl)furo-[2,3,d]pyrimidine (corresponding to a case where R2=methyl in the compound VIII of the Reaction Formula 8). Compounds VIII-1 and VIII-3 to VIII-5 were also each obtained using the same method.

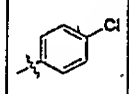
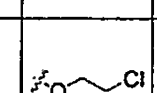
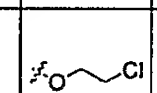
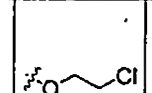
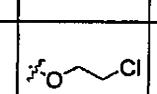
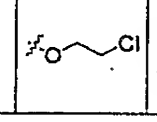
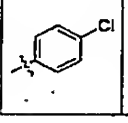
Example 9-2: Preparation of 4-chloro-5-methyl-6-[4-(2-chloroethoxy)phenyl]furo[2,3,d]pyrimidine (IX')

(a) 1.32 ml (7.26 mmol) of 2-chloroethyl para-toluensulfonate was added to a mixture of 859 mg (3.3 mmol) of 4-chloro-5-methyl-6-(4-hydroxyphenyl)furo[2,3,d]pyrimidine (VIII-2) obtained in Example 9-1, 2.37 g (7.26 mmol) of cesium carbonate (Cs_2CO_3) and 5 ml of dimethylformamide, and then stirred at a room temperature for 2 hours. 20 ml of water was applied to the reactant, filtered, and washed with ethylacetate. An organic layer extracted with

ethylacetate twice or three times from the filtrate, dried, condensed, and then, purified by column chromatography to obtain 205 mg of white solid product of 4-chloro-5-methyl-6-[4-(2-chloroethoxy)phenyl]furo[2,3,d]pyrimidine (corresponding to a case where n'=2 in compound IX' of the Reaction Formula 8 : the compound IX of the Reaction Formula 1) (yield: 19%).

(b) 0.067 ml (1 mmol) of 2-chloroethylalcohol was added to a mixture of 130.34 mg (0.5 mmol) of 4-chloro-5-methyl-6-(4-hydroxyphenyl)furo[2,3,d]pyrimidine (VIII-2) obtained in Example 9-1, 262.29 mg (1 mmol) of triphenylphospin (PPh_3) and 1/3 ml of benzene (C_6H_6)/tetrahydrofurane (THF), cooled at 0°C and then stirred for about 10 minutes. 0.097 ml (1 mmol) of diisopropyl azodicarboxylate (DIAD) was applied to the reactant and stirred for 12 hours at a room temperature. 20 ml of salt water (NaCl) was applied to the reactant and an organic layer was extracted with ethylacetate twice or three times. The obtained organic layer was dried, condensed, and then, purified by columnchromatography to obtain 148 mg of white solid product of 4-chloro-5-methyl-6-[4-(2-chloroethoxy)phenyl]furo[2,3,d]pyrimidine (corresponding to a case where n'=2 and R2=methyl in compound IX' of the Reaction Formula 8 : the compound IX of the Reaction Formula 1). Compounds IX-1 and IX-3 to IX-5 of Table 7 were also each obtained using the same method.

[Table 7]

	R	R_2	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)	Yield (%)
VIII-1	OH	H	10.11 (s, 1H), 8.76 (s, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.46 (s, 3H), 6.94 (d, J = 8.4 Hz, 2H)	95
VIII-2	OH	CH_3	10.13 (s, 1H), 8.75 (s, 1H), 7.67 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 2.56 (s, 3H)	89
VIII-3	OH	Br	10.35 (s, 1H), 8.77 (s, 1H), 7.99 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H)	85
VIII-4	OH	Ph	8.71 (s, 1H), 8.71 (s, 1H), 7.58~7.42 (m, 5H), 7.38~7.30 (m, 2H), 6.80~6.72 (m, 2H)	96
VIII-5	OH		10.15 (s, 1H), 8.74 (s, 1H), 7.61 (d, J = 8.4 Hz, 2H),, 7.54 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H)	98
IX-1		H	8.71 (s, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 6.95 (s, 1H), 4.31 (t, J = 6.0 Hz, 2H), 3.86 (t, J = 6.0 Hz, 2H)	96
IX-2		CH_3	^{1}H NMR (400 MHz $CDCl_3$) δ 8.69 (s, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.8 Hz, 2H), 4.32 (t, J = 6.0 Hz, 2H), 3.89 (t, J = 6.0 Hz, 2H), 2.64 (s, 3H)	92
IX-3		Br	^{1}H NMR (400 MHz $CDCl_3$) δ 8.69 (s, 1H), 8.17 (d, J = 9.2 Hz, 2H), 7.06 (d, J = 9.2 Hz, 2H), 4.32 (t, J = 6.0 Hz, 2H), 3.87 (t, J = 6.0 Hz, 2H)	95
IX-4		Ph	8.73 (s, 1H), 7.58~7.42 (m, 7H), 6.88~6.82 (m, 2H), 4.23 (t, J = 5.6 Hz, 2H), 3.80 (t, J = 5.6 Hz, 2H)	93
IX-5			8.68 (s, 1H), 7.53~7.47 (m, 4H), 7.39 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.24 (t, J = 6.0 Hz, 2H), 3.82 (t, J = 6.0 Hz, 2H)	90

Example 9-3: Preparation of 4-(3-hydroxyanilino)-5-methyl-6-[4-(2-chloroethoxy)phenyl]furo[2,3,d]pyrimidine (X')

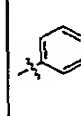
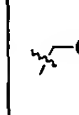
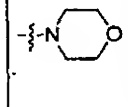
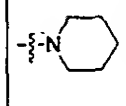
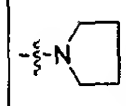
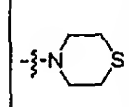
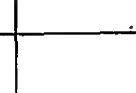
2 ml of n-butylalcohol was applied to 79 mg (0.25 mmol) of 4-chloro-5-methyl-6-[4-(2-chloroethoxy)phenyl]furo[2,3,d]pyrimidine (IX-2) obtained in Example 9-2 and 53.5 mg (0.5 mmol) of 3-aminopenol, and heated and refluxed for 4 hours. After the solvent was removed, water was applied to the resulting mixture, and an organic layer was extracted with ethylacetate twice or three times. The obtained organic layer was dried, condensed, and then, purified by column chromatography to obtain 80 mg of brown solid product of 4-(3-hydroxyanilino)-5-

methyl-6-[4-(2-chloroethoxy) phenyl]furo[2,3,d]pyrimidine (corresponding to a case where n'=2 and R2=methyl in compound X' of the Reaction Formula 8 : the compound X of Reaction Formula 1).

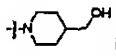
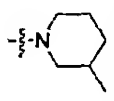
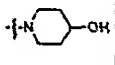
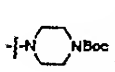
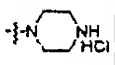
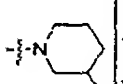
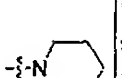
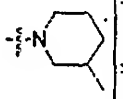
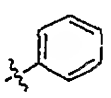
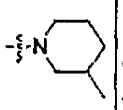
Example 9-4: Preparation of 4-(3-hydroxyanilino)-5-methyl-6-{4-[2-(4-molphorynyl)ethoxy]phenyl}furo[2,3,d]pyrimidine (A-1)

A small amount of 0.07 ml (0.8 mmol) of molphorine was added to 19 mg of 4-(3-hydroxyanilino)-5-methyl-6-[4-(2-chloroethoxy)phenylfuro{2,3,d}pyrimidine (X-2) obtained in Example 9-3 and 7 mg (0.046 mmol) of sodium iodide (NaI), and then, stirred at 90°C for 24 hours. Saturated sodium hydroxy carbon (Na_2HCO_3) aqueous solution was added to the reactant, and an organic layer was extracted with athylacetate twice or three times. The obtained organic layer was dried, condensed, and then, purified by column chromatography to obtain 15 mg of yellow solid product of 4-(3-hydroxyanilino)-5-methyl-6-{4-[2-(4-molphorynyl)ethoxy]phenyl}furo[2,3,d,]pyrimidine (A-1) (yield: 71%). Compounds A-1 and A-3 to A-17 were also each obtained using the same method. Tables 8-1 to 8-3 show analysis results of the thusly obtained compounds.

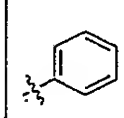
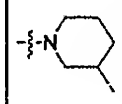
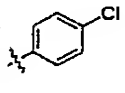
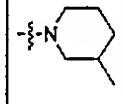
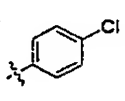
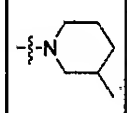
[Table 8-1]

	R_2	R_3	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)		Yield (%)
X-1	H	Cl	9.67 (s, 1H), 9.46 (s, 1H), 8.40 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.45~7.38 (m, 2H), 7.26~7.08 (m, 4H), 6.49 (dd, J = 8.0, 1.2 Hz, 1H), 4.34 (t, J = 5.2 Hz, 2H), 3.99 (t, J = 5.2 Hz, 2H)	132~135	95
X-2	CH_3	Cl	9.42 (s, 1H), 8.51 (s, 1H), 8.36 (s, 1H), 7.69 (d, J = 8.8 Hz, 2H), 7.26~7.04 (m, 5H), 6.52 (d, J = 8.0 Hz, 1H), 4.35 (br t, 2H), 4.00 (br t, 2H), 2.60 (s, 3H)	173~174	89
X-3	Br	Cl	9.49 (s, 1H), 8.52 (s, 1H), 8.39 (s, 1H), 7.58 (d, J = 9.2 Hz, 2H), 7.28~7.02 (m, 5H), 6.57 (dd, J = 8.0, 2.0 Hz, 1H), 4.29 (t, J = 5.2 Hz, 2H), 3.92 (t, J = 5.2 Hz, 2H)	163~166	78
X-4	Ph	Cl	9.50 (s, 1H), 8.51 (s, 1H), 7.71~7.60 (br s, 5H), 7.45 (d, J = 8.8 Hz, 2H), 7.09~6.98 (m, 4H), 6.63 (s, 1H), 6.60 (dd, J = 8.0, 2.0 Hz, 1H), 6.43 (dd, J = 8.0, 2.0 Hz, 1H), 4.27 (t, J = 5.2 Hz, 2H), 3.94 (t, J = 5.2 Hz, 2H)	188~190	76
X-5		Cl	^{1}H NMR (400 MHz $CDCl_3$) δ 8.60 (s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.14 (t, J = 8.0 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 6.63~6.60 (m, 1H), 6.54~6.52 (m, 1H), 6.47 (s, 1H), 4.21 (t, J = 6.0 Hz, 2H), 3.80 (t, J = 6.0 Hz, 2H)	197~199	91
X-6		Cl	^{1}H NMR (400 MHz $CDCl_3$) δ 9.49 (s, 1H), 8.44 (s, 1H), 8.43 (s, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 1.2 Hz, 1H), 7.21~7.16 (m, 4H), 6.62~6.56 (m, 1H), 5.01 (s, 2H), 4.42 (t, J = 5.2 Hz, 2H), 3.99 (t, J = 5.2 Hz, 2H), 3.65 (s, 1H)	134~135	52
A-1	CH_3		9.42 (s, 1H), 8.50 (s, 1H), 8.36 (s, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.24~7.00 (m, 5H), 6.51 (d, J = 8.0 Hz, 1H), 4.17 (t, J = 5.6 Hz, 2H), 3.59 (t, J = 4.0 Hz, 2H), 2.73 (t, 2H), 2.59 (s, 3H), 2.50 (br t, 4H)	200~201	88
A-2	CH_3		9.39 (s, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 7.66 (d, J = 8.8 Hz, 2H), 7.21~6.98 (m, 5H), 6.51 (dd, J = 8.0, 1.2 Hz, 1H), 4.14 (t, J = 6.4 Hz, 2H), 2.68 (t, J = 6.4 Hz, 2H), 2.58 (s, 3H), 2.44~2.36 (m, 4H), 1.61~1.31 (m, 6H)	211~213	74
A-3	CH_3		^{1}H NMR (400 MHz $CDCl_3$) δ 8.29 (s, 1H), 7.73 (s, 1H), 7.40 (d, J = 8.8 Hz, 2H), 7.23 (t, J = 8.0 Hz, 1H), 6.87~6.74 (m, 4H), 6.64 (dd, J = 8.0, 2.4 Hz, 1H), 4.18 (t, J = 5.6 Hz, 2H), 2.74~2.62 (m, 4H), 2.53 (s, 3H), 1.80~1.68 (m, 4H)	198~200	66
A-4	CH_3		9.41 (s, 1H), 8.50 (s, 1H), 8.35 (s, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.21~7.02 (m, 5H), 6.51 (dd, J = 8.0, 1.6 Hz, 1H), 4.15 (t, J = 5.6 Hz, 2H), 2.80~2.72 (m, 6H), 2.64~2.51 (m, 4H), 2.58 (s, 3H)	221~225	79
A-5	CH_3		^{1}H NMR (400 MHz $CDCl_3$) δ 8.34 (s, 1H), 7.66~7.62 (m, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.23 (t, J = 8.0 Hz, 1H), 6.88~6.76 (m, 4H), 6.64 (dd, J = 8.0, 1.6 Hz, 1H), 4.15 (d, J = 5.6 Hz, 2H), 2.89 (t, J = 5.6 Hz, 2H), 2.86~2.42 (m, 8H), 2.52 (s, 3H), 2.35 (s, 3H)	223~227	42

[Table 8-2]

	R_2	R_3	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)	mp	Yield (%)
A-6	CH_3		^{1}H NMR (400 MHz D_2O) δ 8.41 (s, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.32~7.28 (m, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.09 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.02 (d, *J* = 6.4 Hz, 2H), 6.65 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.20 (t, *J* = 6.0 Hz, 2H), 3.45 (d, *J* = 6.4 Hz, 2H), 3.14~3.00 (m, 2H), 2.89 (t, *J* = 6.0 Hz, 2H), 2.61 (s, 3H), 2.26~2.14 (m, 2H), 1.82~1.71 (m, 2H), 1.62~1.28 (m, 3H)	227~229	35
A-7	CH_3		9.42 (s, 1H), 8.50 (s, 1H), 8.36 (s, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.21~7.03 (m, 5H), 6.52 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.15 (t, *J* = 6.0 Hz, 2H), 2.94~2.80 (m, 2H), 2.70 (t, *J* = 6.0 Hz, 2H), 2.59 (s, 3H), 2.01~1.89 (m, 1H), 1.72~1.42 (m, 6H), 0.83 (d, *J* = 6.8 Hz, 3H)	225~229	78
A-8	CH_3		9.44 (s, 1H), 8.50 (s, 1H), 8.35 (s, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.24~7.02 (m, 5H), 6.52 (dd, *J* = 7.6, 1.6 Hz, 1H), 4.57 (d, *J* = 4.0 Hz, 1H), 4.13 (t, *J* = 6.0 Hz, 2H), 3.52~3.46 (m, 1H), 2.87~2.75 (m, 2H), 2.69 (t, *J* = 6.0 Hz, 2H), 2.58 (s, 3H), 2.21~2.08 (m, 2H), 1.79~1.68 (m, 2H), 1.45~1.34 (m, 2H)	214~218	52
A-9	CH_3		^{1}H NMR (400 MHz $CDCl_3$) δ 8.40 (s, 1H), 7.62~7.58 (m, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.23 (t, *J* = 8.0 Hz, 1H), 6.89~6.76 (m, 3H), 6.66 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.15 (t, *J* = 5.2 Hz, 2H), 3.56~3.46 (m, 4H), 2.87 (t, *J* = 5.2 Hz, 2H), 2.66~2.58 (m, 4H), 2.53 (s, 3H), 1.47 (s, 9H)	216~218	83
A-10	CH_3		12.32~11.92 (br s, 1H), 9.84~9.68 (br s, 2H), 8.59 (s, 1H), 8.36 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.23~7.02 (m, 5H), 6.54 (dd, *J* = 8.0, 2.4 Hz, 1H), 4.52 (t, *J* = 4.8 Hz, 2H), 3.74~3.36 (m, 10H), 2.59 (s, 3H)	201~205	74
A-11	H		9.67 (s, 1H), 9.46 (s, 1H), 8.41 (s, 1H), 8.33 (s, 1H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.45~7.38 (m, 2H), 7.25~7.10 (m, 4H), 6.50 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.27 (t, *J* = 6.0 Hz, 2H), 3.26~3.12 (m, 2H), 2.73 (t, *J* = 6.0 Hz, 2H), 1.81~1.50 (m, 7H), 0.88 (d, *J* = 6.6 Hz, 3H)	176~179	52
A-12	Br		9.51 (s, 1H), 8.56 (s, 1H), 8.35 (s, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.18~7.05 (m, 5H), 6.50 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.17 (t, *J* = 5.2 Hz, 2H), 2.88~2.77 (m, 2H), 2.73 (t, *J* = 6.0 Hz, 2H), 2.01~1.92 (m, 1H), 1.74~1.43 (m, 6H), 0.85 (d, *J* = 6.8 Hz, 3H)	184~187	59
A-13			9.53 (s, 1H), 8.51 (s, 1H), 8.47 (s, 1H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 1.2 Hz, 1H), 7.23~7.16 (m, 4H), 6.61~6.54 (m, 1H), 5.07 (s, 2H), 4.45 (t, *J* = 5.2 Hz, 2H), 3.63 (s, 3H), 2.93~2.81 (m, 2H), 2.72 (t, *J* = 5.2 Hz, 2H), 2.00~1.87 (m, 1H), 1.73~1.41 (m, 6H), 0.82 (d, *J* = 6.8 Hz, 3H)	199~203	71
A-14			9.51 (s, 1H), 8.51 (s, 1H), 7.76~7.60 (br s, 5H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.10~7.00 (m, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.63 (s, 1H), 6.59 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.43 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.06 (t, *J* = 6.0 Hz, 2H), 2.62 (t, *J* = 6.0 Hz, 2H), 2.62 (t, *J* = 6.0 Hz, 2H), 2.45~2.34 (m, 4H), 1.52~1.45 (m, 4H), 1.40~1.32 (m, 2H)	231~234	85

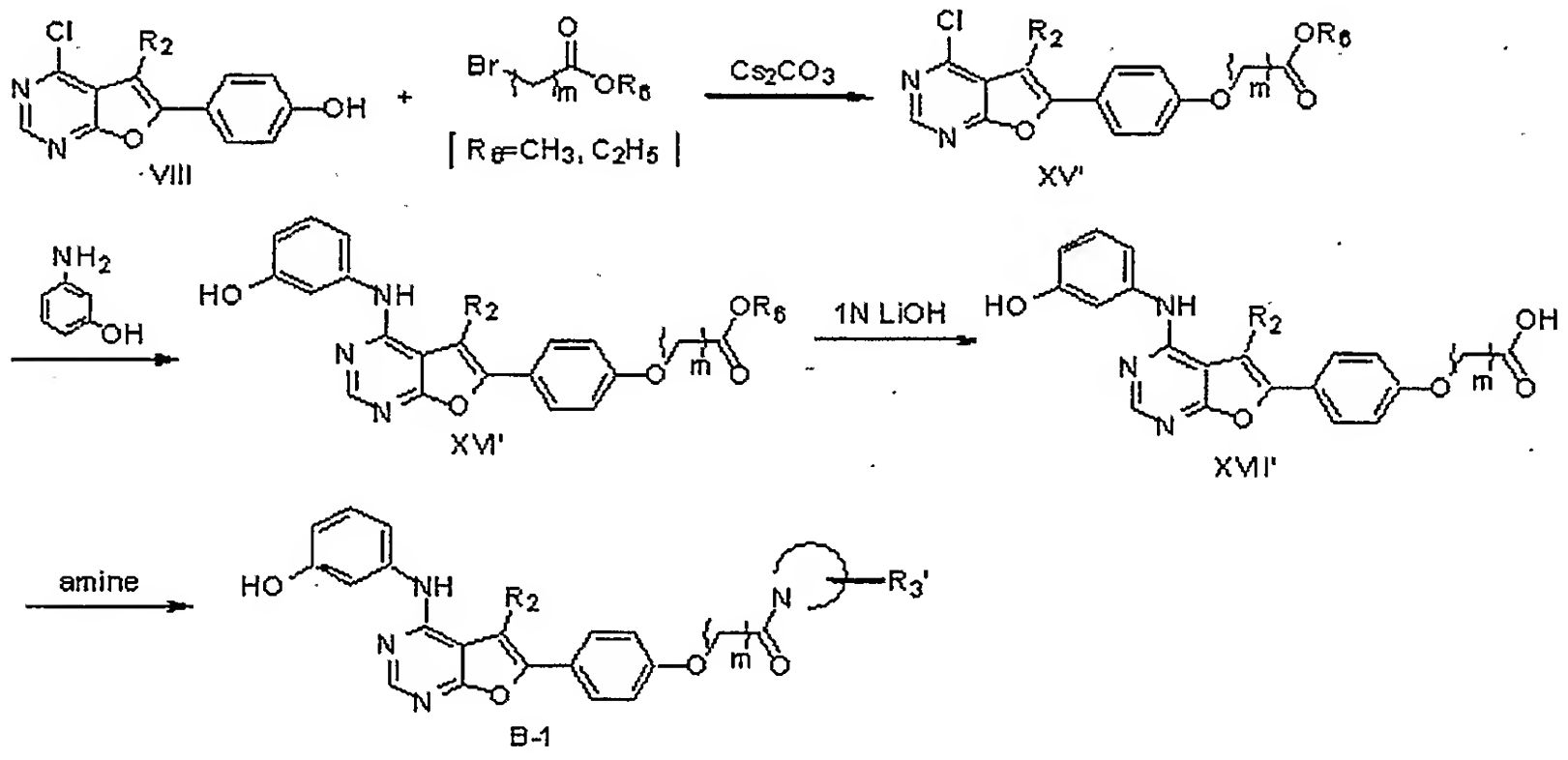
[Table 8-3]

	R_2	R_3	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)	mp	Yield (%)
A-15			9.50 (s, 1H), 8.51 (s, 1H), 7.74~7.60 (br s, 5H), 7.42 (d, J = 8.8 Hz, 2H), 7.09~7.00 (m, 2H), 6.96 (d, J = 8.8 Hz, 2H), 6.64~6.58 (m, 2H), 6.43 (dd, J = 8.0, 2.4 Hz, 1H), 4.07 (t, J = 6.0 Hz, 2H), 2.90~2.78 (m, 2H), 2.64~(t, J = 6.0 Hz, 2H), 1.96~1.86 (m, 1H), 1.70~1.36 (m, 6H), 0.81 (d, J = 6.4 Hz, 3H)	223~228	64
A-16			9.48 (s, 1H), 8.49 (s, 1H), 7.70~7.63 (m, 4H), 7.38 (d, J = 8.8 Hz, 2H), 7.07 (t, J = 8.0 Hz, 1H), 7.02 (s, 1H), 6.98 (d, J = 8.8 Hz, 2H), 6.90 (s, 1H), 6.71 (d, J = 7.6 Hz, 1H), 6.45 (d, J = 7.6 Hz, 1H), 4.07 (t, J = 6.0 Hz, 2H), 2.63 (t, J = 6.0 Hz, 2H), 2.41~2.39 (m, 4H), 1.49~1.46 (m, 4H), 1.37~1.36 (m, 2H)	226~227	74
A-17			^{1}H NMR (400 MHz $CDCl_3$) 8.30 (s, 1H), 7.63~7.61 (m, 3H), 7.54 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.26 (s, 1H), 7.12 (t, J = 8.0 Hz, 1H), 6.68 (d, J = 8.8 Hz, 2H), 6.60~6.56 (m, 1H), 6.40 (s, 1H), 6.25 (dd, J = 8.0, 1.2 Hz, 1H), 4.13 (t, J = 5.2 Hz, 2H), 3.79 (t, J = 4.4 Hz, 4H), 2.85 (t, J = 5.2 Hz, 2H), 2.69~2.67 (m, 4H)	226~230	60

[Example 10]

A compound "B," a precursor of the compounds of the present invention, can be prepared by using the thusly-obtained compound VIII, for example, according to the following Reaction Formula 9.

[Reaction Formula 9]



Example 10-1: Preparation of 4-chloro-5-methyl-6-[4-(methyl 2-acetoxy)phenyl]furo{2,3,d}pyrimidine (XV'-1)

336.5 mg (2.2 mmol) of methyl 2-bromoacetophenon was added to a mixture of 260.68 mg (1 mmol) of 4-chloro-5-methyl-6-(4-hydroxyphenyl)furo[2,3,d]pyrimidine (VIII-2) obtained in Example 9-1, 716.8 g (2.2 mmol) of cesium carbonate (Cs_2CO_3) and 5 ml of dimethylformamide, and then stirred at 60°C for 2 hours. 20ml of water was applied to the reactant, filtered, and then, washed with ethylacetate. An organic layer was extracted with ethylqcetate twice or three times from the filtrate, dried, condensed, and then, purified by column chromatography to obtain 296 mg of white solid product of 4-chloro-5-methyl-6-[4-(methyl 2-acetoxy)phenyl]furo[2,3,d]pyrimidine (corresponding to a case where m=1, R2=methyl and R6=methyl in compound XV' of the Reaction Formula 9 : the compound XV of the Reaction Formula 1). (Yield: 89%). A compound XV'-2 (corresponding to a case where m=1, R2=(4-chlorophenyl) and R6=methyl in the compound XV' of the Reaction Formula 9 : the compound XV of the Reaction Formula 1) was obtained according to the same method.

^{1}H NMR (400 MHz $CDCl_3$) δ (ppm) 8.68 (s, 1H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 4.72 (s, 2H), 3.84 (s, 3H), 2.61 (s, 3H)

Compound XV'-2 : ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm) 8.66 (s, 1H), 7.51~7.41 (m, 4H), 7.34 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 4.60 (s, 2H), 3.75 (s, 3H)

Example 10-2: Preparation of 4-(3-hydroxyanilino)-5-methol-6-[4-methyl 2-acetoxy]phenyl]furo[2,3,d]pyrimidine (XVI'-1)

2 ml of n-butylalcohol was applied to 83.18 mg (0.25 mmol) of 4-chloro-5-methyl-6-[4-(methyl 2-acetoxy)phenyl]furo[2,3,d]pyrimidine (XVI'-1) obtained in Example 10-1 and 53.5 mg (0.5 mmol) of 3-aminophenol, and heated and refluxed for 4 hours. After the solvent was removed, water was applied thereto, and an organic layer was extracted with ethylacetate twice or three times. The obtained organic layer was dried, condensed, and then, purified by column chromatography to obtain a 73 mg of brown solid product of 4-(3-hydroxyanilino)-5-methyl-6-(4-(methyl 2-acetoxy)phenyl)furo[2,3,d]pyrimidine (corresponding to a case where m=1, R2=methyl and R6=methyl in compound XVI' of Reaction Formula 9 : the compound XVI of Reaction Formula 1). (Yield: 72%). A compound XVI'-2 (corresponding to a case where m=1, R2=(4-chlorophenyl) and R6=methyl in the compound XVI' of Reaction Formula 9 : the compound XVI of the Reaction Formula 1) was obtained according to the same method.

^{1}H NMR (400 MHz DMSO-d_6) δ (ppm) 9.43 (s, 1H), 8.51 (s, 1H), 8.34 (s, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.26~7.00 (m, 5H), 6.52 (d, J = 8.0, 2.0 Hz, 1H), 4.90 (s, 2H), 3.73 (s, 3H), 2.60 (s, 3H)

Compound XVI '-2 : ^{1}H NMR (400 MHz DMSO-d_6) δ (ppm) 9.48 (s, 1H), 8.49 (s, 1H), 7.71~7.65 (m, 4H), 7.08 (d, J = 8.8 Hz, 2H), 7.07 (t, J = 0.8 Hz, 1H), 7.02~6.97 (m, 3H), 6.90 (s, 1H), 6.71 (d, J = 7.6 Hz, 1H), 6.45 (d, J = 7.6 Hz, 1H), 4.84 (s, 2H), 3.70 (s, 3H)

Example 10-3: Preparation of 4-(3-hydroxyanilino)-5-(4-chlorophenyl)-6-[4-(carboxylicmethoxy)phenyl]furo[2,3,d]pyrimidine (XV1'-2)

0.5 ml of tetrahydrofuran (THF) was added dropwisely to 24 mg (0.047 mmol) of 4-(3-hydroxyanilino)-5-(4-chlorophenyl)-6-[4-(methyl 2-

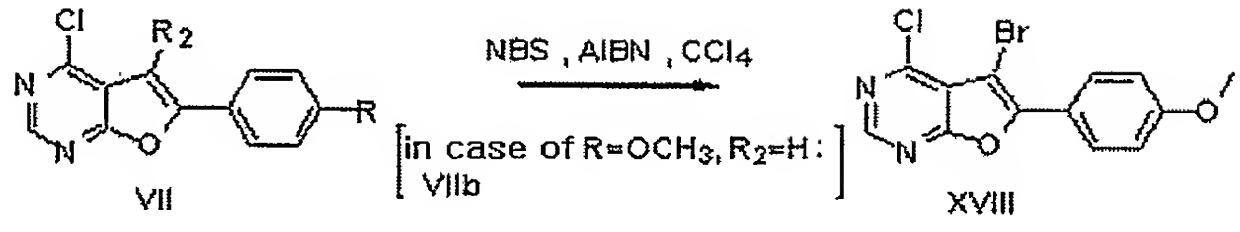
acetoxy)phenyl]furo[2,3,d]pyrimidine (XVI'-2) obtained in Example 10-2, to which 0.056 ml (0.056 mmol) of 0.1N-LiOH was slowly applied dropwisely at 0°C and then stirred for 1 hour at a room temperature. Water (1 ml) was added to the reactant, washed with ethylacetate (1 ml) twice or three times, neutralized with 0.061 ml (0.061 mmol) of 1N-hydrochloric acid aqueous solution, and then, extracted with ethylacetate twice or three times. The resultant solution was dried and then condensed to obtain 21 mg of compound 4-(3-hydroxyanilino)-5-(4-chlorophenyl)-6-[4-(carboxylicmethoxy)phenyl]furo[2,3,d]pyrimidine (XVII'-2) (yield: 99%) (corresponding to a case where m=1, R2=(4-chlorophenyl) and R6=methyl in the compound XVII' of the Reaction Formula 9 : the compound XVII of Reaction Formula 1). A compound XVII'-1 was also obtained using the same method.

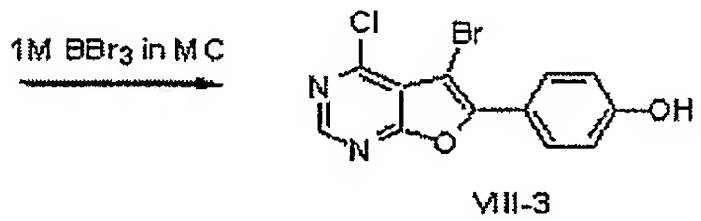
^{1}H NMR (400 MHz DMSO-d_6) δ (ppm) 9.50 (s, 1H), 8.50 (s, 1H), 7.70~7.64 (m, 4H), 7.39 (d, J = 8.8 Hz, 2H), 7.07 (t, J = 0.8 Hz, 1H), 7.01 (s, 1H). 6.95 (d, J = 8.8 Hz, 2H), 6.91 (s, 1H), 6.71 (d, J = 7.6 Hz, 1H), 6.44 (dd, J = 8.0, 1.2 Hz, 1H), 4.68 (s, 2H)

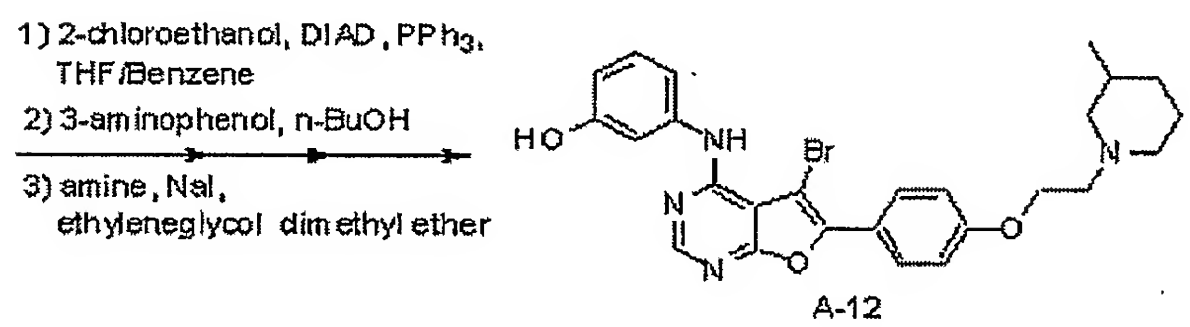
Example 11

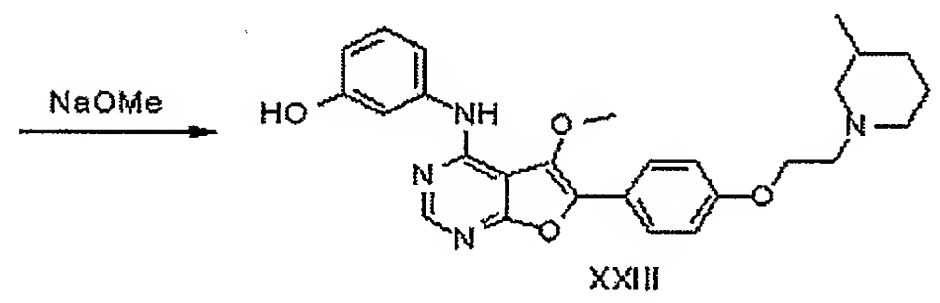
A compound XXIII, a precursor of the compounds of the present invention, can be prepared by using the thusly obtained compound VII, for example, according to the following Reaction Formula 10.

[Reaction Formula 10]









Example 11-1: Preparation of 4-chloro-5-bromo-6-(4-methoxyphenyl)furo[2,3,d]pyrimidine (XVIII)

25 ml of carbontetrachloride was added to 380 mg (1.46 mmol) of 4-chloro-6-(4-methoxyphenyl)furo[2,3,d]pyrimidine (VIIb) obtained in Example 7, 359.23 mg (1.53 mmol) of N-bromosuccinimide and 47.5 mg (0.146 mmol) of α,α'-azobis (isobutylonitril), and stirred and refluxed for 12 hours. The resulting mixture was cooled at a room temperature, condensed, and then, purified by column chromatography to obtain 230 mg of 4-chloro-5-bromo-6-(4-methoxyphenyl)furo[2,3,d]pyrimidine (XVIII) (yield: 55%).

^{1}H NMR (400 MHz $CDCl_3$) δ (ppm) 8.73 (s, 1H), 8.16 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 3.90 (s, 3H)

Example 11-2: 4-chloro-5-bromo-6-(4-hydroxyphenyl)furo[2,3,d]pyrimidine (VIII-3)

4-chloro-5-bromo-6-(4-hydroxyphenyl)furo[2,3,d]pyrimidine (VIII-3) was obtained by proceeding in the same manner as Example 9-1.

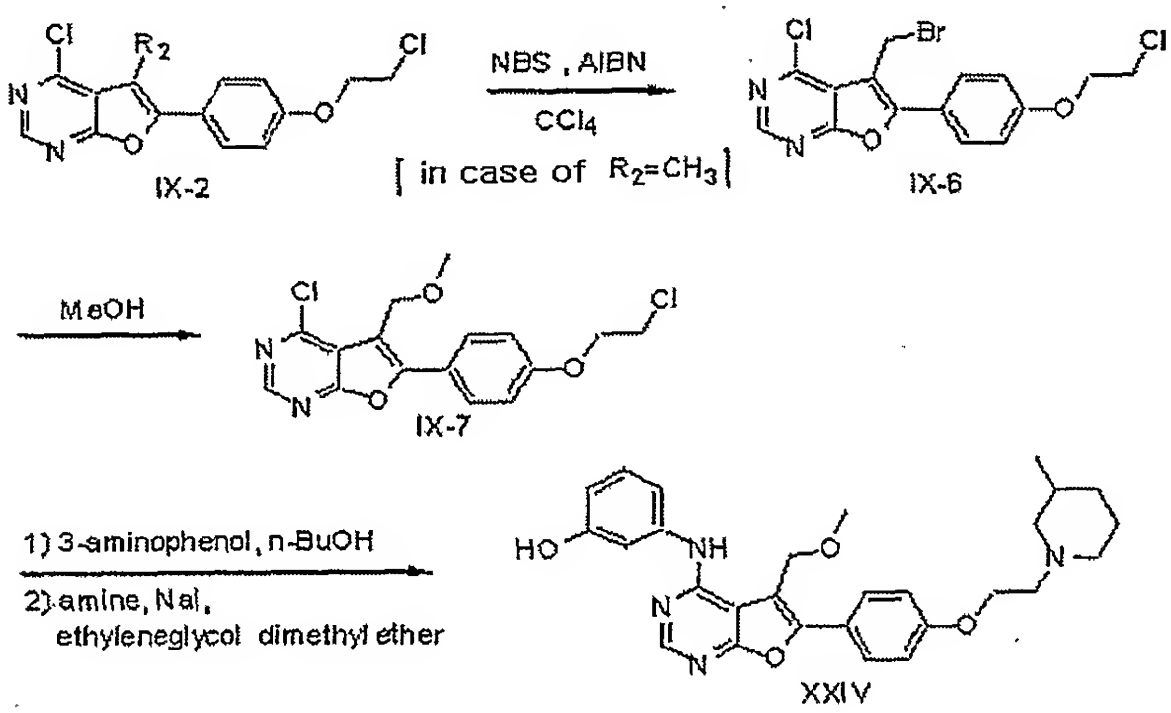
Table 7 shows analysis results of the thusly-obtained compound.

Example 11-3: Preparation of 4-(3-hydroxyanilino)-5-bromo-6-{4-[3-(3-methylpiperidinyl)ethoxy]phenyl}furo[2,3,d]pyrimidine (A-12)

4-(3-hydroxyanilino)-5-bromo-6-{4-[2-(3-methylpiperidinyl)ethoxy]phenyl}furo[2,3,d]pyrimidine (A-12) was obtained by sequentially performing Examples 9-2, 9-3 and 9-4.

Tables 8-1 and 8-2 show analysis results of the thusly obtained compound.

[Reaction Formula 11]



[Example 12]

Example 12-1: Preparation of 4-chloro-5-bromomethyl-6-[4-(2-chloroethoxy)phenyl]furo{2,3,d}pyrimidine (IX-6)

Example 12-1 was performed in the same manner as Example 11-1 by using 4-chloro-5-methyl-6-[4-(2-chloroethoxy)phenyl]furo{2,3,d}pyrimidine (IX-2) obtained in Example 9-1.

^{1}H NMR (400 MHz $CDCl_3$) δ (ppm) 8.71 (s, 1H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 4.89 (s, 2H), 4.34 (t, *J* = 6.0, 2H), 3.88 (t, *J* = 6.0, 2H),

Example 12-2: Preparation of 4-chloro-5-methoxymethyl-6-[4-(2-chloroethoxy)phenyl]furo[2,3,d]pyrimidine (IX-7)

15 ml of methylalcohol was added to 160 mg (0.04 mmol) of 4-chloro-5-methyl-6-[4-(2-chloroethoxy)phenyl]furo[2,3,d]pyrimidine (IX-6) obtained in Example 9-1, and stirred and refluxed for 6 hours. The solution was condensed and then purified by column chromatography to obtain a 73 mg of white solid of 4-chloro-5-methoxymethyl-6-[4-(2-chloroetnoxy)phenyl]furo[2,3,d]pyrimidine (IX-7) (yield: 52%) and 60 mg of 4-methoxy-5-methoxymethyl-6-[4-(2-chloroethoxy)phenyl]furo[2,3,d]pyrimidine (IX-7-1) as a by-product (yield: 43%).

Compound IX-7: ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm) 8.67 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 4.75 (s, 2H), 4.32 (t, *J* = 6.0, 2H), 3.87 (t, *J* = 6.0, 2H), 2.58 (s, 3H)

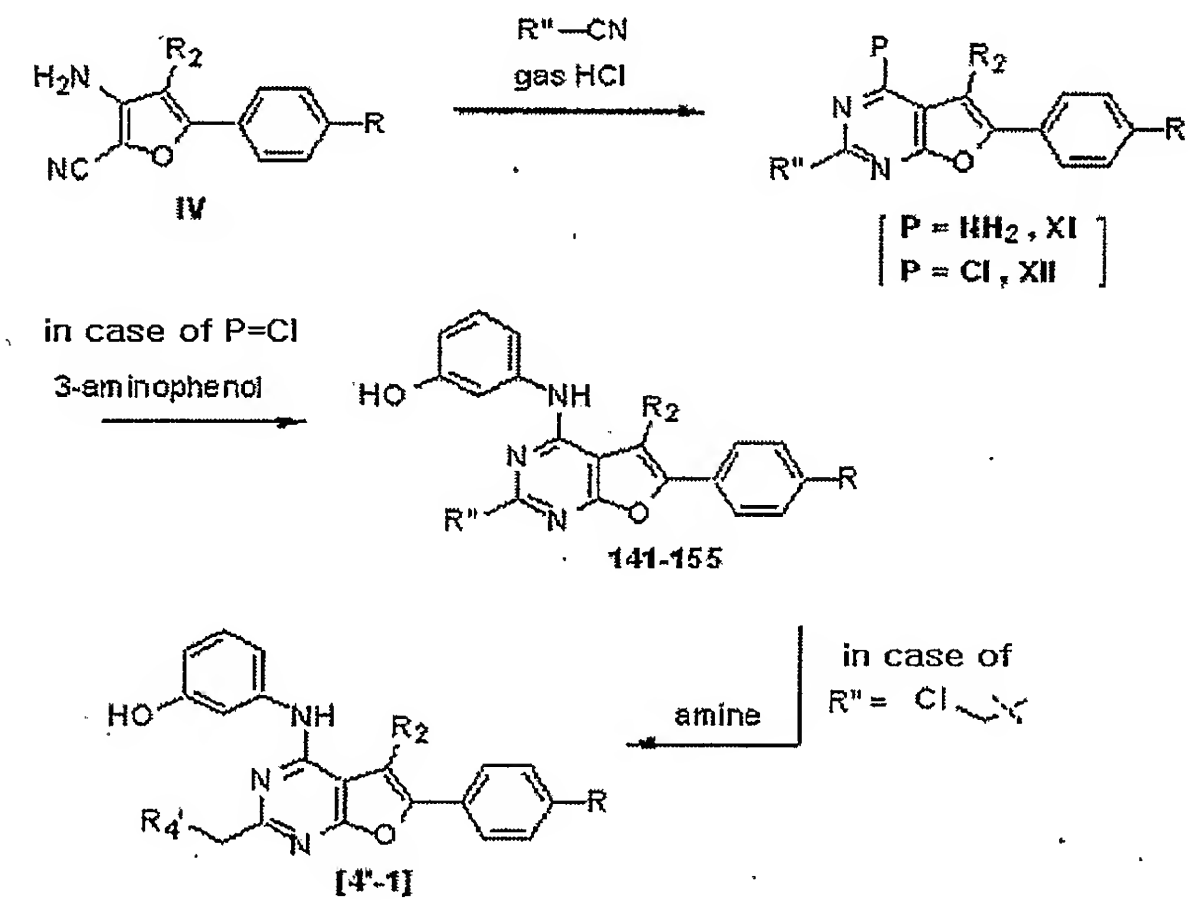
Compound IX-7-1: ^{1}H NMR (400 MHz $CDCl_3$) δ (ppm) 8.52 (s, 1H), 7.86 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 4.70 (s, 2H), 4.30 (t, *J* = 6.0, 2H), 4.17 (s, 3H), 3.86 (t, *J* = 6.0, 2H), 3.50 (s, 3H)

Example 12-3: Preparation of 4-(3-hydroxyanilino)-5-methoxymethyl-6-{4-[2](3-methylpiperidinyl)ethoxy]phenyl}furo[2,3,d]pyrimidine (A-12)

4-(3-hydroxyanilino)-5-methoxymethyl-6-{4-[2-(3-methylpiperidinyl)ethoxy]phenyl}furo[2,3,d]pyrimidine (A-13) was obtained by sequentially performing Examples 9-3 and 9-4.

Tables 8-1 and 8-2 show analysis results of the thusly obtained compound.

[Reaction Formula 12]



Example 13: Preparation of 2,4,5,6-substituted furopyrimidine-based compound

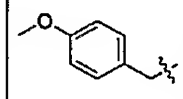
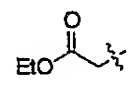
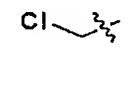
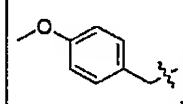
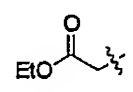
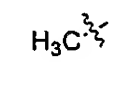
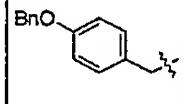
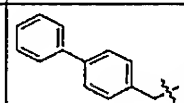
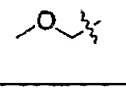
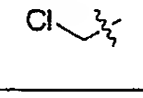
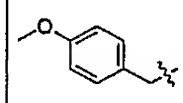
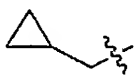
Example 13-1: 2-chloromethyl-4-chloro-5-methyl-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (XII-A)

2.32g (10 mmol) of 2-amino-3-cyano-5-(4-chlorophenyl)furan(IVd) obtained in Example 5 was diluted in 30 ml of dioxane, to which 0.69 ml (11

mmol) of chloroacetonitril was applied dropwisely. The reaction solution was stirred while continuously generating a hydrochloric acid gas in the reaction solution at a room temperature for 6 hours, and then left as it is for 12 hours. 100 ml of water was applied to the reaction solution to generate a solid. The generated solid was filtered, sufficiently washed with water and n-hexane, and then, dried to obtain 544 g of white solid of 2-chloromethyl-4-amino-5-methyl-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (XI-A) (yield: 17%). 15 ml of 10% ammonia aqueous solution was applied to the filtrate, extracted with ethylacetate twice or three times, dried, condensed, and then, purified by columnchromatography to obtain 2.09g of light yellow solid of 2-chloromethyl-4-chloro-5-methyl-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (XII-A). Compounds XI-B~XI-C to XII-B~XII-L of Table 7 were also obtained, respectively, according to the same method. In case where R" is hydrogen, Examples 6 and 7 were sequentially performed to obtain compounds VI and VII.

Table 9 shows analysis results of the thusly obtained compounds.

[Table 9]

	R	R_2	P	R"	^{1}H NMR (400 MHz $CDCl_3$) δ (ppm)	mp(℃)	Yield (%)
XI-B	Cl	CH_3	NH_2		^{1}H NMR (400 MHz DMSO-d_6) δ 7.70 (d, J = 8.4 Hz, 2H), δ 7.56 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.24~7.08 (br s, 2H), 3.89 (s, 2H), 3.70 (s, 3H), 2.49 (s, 3H)	196~197	26
XI-C	Cl	CH_3	NH_2		7.60 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 5.51~5.61 (br s, 2H), 4.22 (d, J = 7.2 Hz, 2H), 3.86 (s, 2H), 2.52 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H)	209~210	17
XII-A	Cl	CH_3	Cl		^{1}H NMR (400 MHz DMSO-d_6) δ 7.85 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 4.91 (s, 2H), 2.59 (s, 3H)	129~130	64
XII-B	Cl	CH_3	Cl		7.70 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 4.26 (s, 2H), 3.78 (s, 3H), 2.61 (s, 3H)	198~199	56
XII-C	Cl	CH_3	Cl		7.73 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H), 4.07 (s, 2H), 2.65 (s, 3H) 1.28 (t, J = 7.2 Hz, 3H)	130~131	37
XII-D	Cl	CH_3	Cl		7.72 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 2.79 (s, 3H), 2.63 (s, 3H)	120~121	21
XII-F	Cl	CH_3	Cl		7.68 (d, J = 8.8 Hz, 2H), 7.46~7.33 (m, 9H), 6.91 (d, J = 8.8 Hz, 2H), 5.02 (s, 2H), 4.25 (s, 2H), 2.59 (s, 3H)	192~193	2.3
XII-G	Cl	CH_3	Cl		7.70 (d, J = 8.8 Hz, 2H), 7.58~7.42 (m, 11H), 4.37 (s, 2H), 2.61 (s, 3H)	175~178	20
XII-H	Cl	CH_3	Cl		7.71 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 4.45 (s, 2H), 3.57 (s, 3H), 2.64 (s, 3H)	127~129	17
XII-I	OCH_3	CH_3	Cl		7.74 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 4.78 (s, 2H), 3.89 (s, 3H), 2.64 (s, 3H)	129~130	53
XII-J	OCH_3	CH_3	Cl		7.71 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H),7.02 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 4.25 (s, 2H), 3.88 (s, 3H) 3.77 (s, 3H), 2.59 (s, 3H)	163~164	50
XII-L	OCH_3	CH_3	Cl		^{1}H NMR (400 MHz DMSO-d_6) δ 7.72 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 2.91 (d, J = 7.6 Hz, 2H), 2.60 (s, 3H), 1.34~1.29 (m, 1H), 0.57~0.52 (m, 2H), 0.34~0.30 (m, 2H)	132~134	5.8

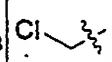
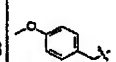
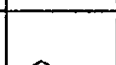
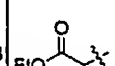
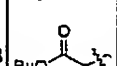
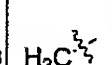
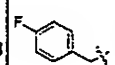
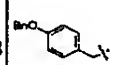
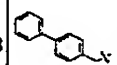
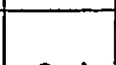
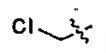
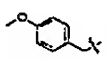
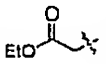
Example 13-2: 2-chloromethyl-4-(3-hydroxyanilino)-5-methyl-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (141)

3 ml of n-butylalcohol was applied dropwisely to 163.8 mg (0.5 mmol) of

2-chloromethyl-4-chloro-5-methyl-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (XII-A) obtained in Example 13-1 and 109.13 mg (1 mmol) of 3-aminophenol, and heated and refluxed for 4 hours, from which the solvent was then removed. The resultant mixture was dissolved in 1 ml of eimethylsulfoxide and filtered by applying 20 ml of water, washed sufficiently with water and n-hexane, and then, dried to obtain an off-white solid product of 2-chloromethyl-4-(3-hydroxyanilino)-5-methyl-6-(4-chlorophenyl)furo[2,3,d]pyrimidine (141). Compounds 142 to 155 were also obtained, respectively, according to the same method.

Tables 10 shows analysis results of the thusly-obtained 2,4,5,6-substitued furopyrimidine-based compounds.

[Table 10]

	R	R_2	R"	^{1}H NMR (400 MHz DMSO-d_6) δ (ppm)	mp	Yield (%)
141	Cl	CH_3		9.44 (s, 1H), 8.65 (s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.26~7.10 (m, 3H), 6.55~6.51 (m, 1H), 4.68 (s, 2H), 2.61 (s, 3H)	187~189	41
142	Cl	CH_3		9.41 (s, 1H), 8.46 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H), 7.24~7.18 (m, 1H), 7.14~7.07 (m, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.55~6.47 (m, 1H), 3.99 (s, 2H), 3.71 (s, 3H), 2.58 (s, 3H)	243~244	33
143	Cl	CH_3		^{1}H NMR (400 MHz CD_3OD) δ 7.74 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.36~7.32 (m, 1H), 7.21~7.06 (m, 2H), 6.59~6.55 (m, 1H), 3.90 (s, 2H), 3.69 (t, J = 5.6 Hz, 2H), 2.81 (t, J = 5.6 Hz, 2H), 2.63 (s, 3H)	209210	24
144	Cl	CH_3		9.39 (s, 1H), 8.52 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.27~7.06 (m, 3H), 6.54~6.46 (m, 1H), 3.65~3.52 (m, 6H), 2.60 (s, 3H), 2.56~2.48 (m, 4H)	257258	21
145	Cl	CH_3		9.38 (s, 1H), 8.54 (s, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.18~7.04 (m, 3H), 6.51 (d, J = 7.2 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 2.60 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H)	211~212	35
146	Cl	CH_3		9.40 (s, 1H), 8.56 (s, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.22~7.02 (m, 3H), 6.53~6.46 (m, 1H), 4.08 (t, J = 6.4 Hz, 2H), 3.82 (s, 2H), 2.60 (s, 3H), 1.61~1.48 (m, 2H), 1.36~1.20 (m, 2H), 0.84 (t, J = 7.6 Hz, 3H)	186~187	32
147	Cl	CH_3		9.41 (s, 1H), 8.46 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 2.0 Hz, 1H), 7.16~7.02 (m, 2H), 6.53~6.44 (m, 1H), 2.58 (s, 3H), 2.49 (s, 3H).	190~191	27
148	Cl	CH_3		9.41 (s, 1H), 8.48 (s, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.40~7.31 (m, 2H), 7.21~7.02 (m, 5H), 6.50 (d, J = 6.8 Hz, 1H), 4.06 (s, 2H), 2.58 (s, 3H)	201~202	53
149	Cl	CH_3		9.40 (s, 1H), 8.46 (s, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 7.6 Hz, 2H), 7.32 (d, J = 7.2 Hz, 1H), 7.25 (d, J = 8.8 Hz, 2H), 7.22 (s, 1H), 7.09 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.0 Hz, 2H), 6.50 (dd, J = 8.0, 1.2 Hz, 1H), 5.06 (s, 2H), 3.99 (s, 2H), 2.58 (s, 3H)	216~218	29
150	Cl	CH_3		9.42 (s, 1H), 8.50 (s, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.65~7.58 (m, 5H), 7.47~7.43 (m, 3H), 7.34 (t, J = 8.0 Hz, 1H), 7.24 (s, 1H), 7.10 (d, J = 8.8 Hz, 2H), 6.51 (d, J = 6.8 Hz, 1H), 4.12 (s, 2H), 2.59 (s, 3H)	208~210	20
151	Cl	CH_3		9.42 (s, 1H), 8.55 (s, 1H), 7.75 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.23 (s, 1H), 7.15~7.13 (m, 2H), 6.54~6.51 (m, 1H), 4.45 (s, 2H), 3.39 (s, 3H), 2.60 (s, 3H)	219~225	56
152	OCH_3	CH_3		9.43 (s, 3H), 8.58 (s, 1H), 7.69 (d, J = 8.8 Hz, 2H), 7.26~7.01 (m, 5H), 6.56~6.47 (m, 1H), 4.68 (s, 2H), 3.84 (s, 3H), 2.57 (s, 3H)	151~152	50
153	OCH_3	CH_3		9.36 (s, 1H), 8.41 (s, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.22 (s, 1H), 7.18~7.01 (m, 4H), 6.53~6.42 (m, 1H), 3.99 (s, 2H), 3.82 (s, 3H), 3.71 (s, 3H), 2.54 (s, 3H)	204~205	54
154	OCH_3	CH_3		9.39 (s, 1H), 8.49 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.21~7.00 (m, 5H), 6.50 (d, J = 8.0 Hz, 1H), 4.13 (q, J = 6.8 Hz, 2H), 3.83 (s, 3H), 2.57 (s, 3H), 1.19 (t, J = 6.8 Hz, 3H)	165~166	34
155	OCH_3	CH_3		9.37 (s, 1H), 8.37 (s, 1H), 7.66 (d, J = 8.8 Hz, 2H), 7.29 (s, 1H), 7.18~7.09 (m, 4H), 6.48 (dd, J = 8.0, 1.2 Hz, 1H), 3.83 (s, 3H), 2.64 (d, J = 6.8 Hz, 2H), 2.57 (s, 3H), 1.22~1.18 (m, 1H), 0.52~0.47 (m, 2H), 0.26~0.22 (m, 2H)	207~210	99

II. Biological activity evaluation of compounds of the present invention

Experimentation of biological activity evaluation of DDR2 with respect to the obtained compounds as described above will be described as follows.

Example 14: Measurement of inhibiting activity with respect to tyrosine kinase activity of DDr2 protein of the compounds of the present invention

2 ug of poly (D4Y)n (Promega, USA) or histone H2B protein at which biotin was attached as a peptide substrate was used to be reacted in a 20 ul of a mixture solution of Tris-HCl (pH 7.5), 5 mM of MgCl2 100 ng of activated DDR2 kinase enzyme protein (prepared according to the method disclosed in Korean Patent Application Nos. 2002-0067233 and 2003-0076967) for 10 to 30 minutes, to which a 30% phosphoric acid solution with 1/2 volume was applied to finish the reaction.

In case where the reactant uses the biotin-attached poly (D4Y)n as the peptide substrate, it was spotted on an abidin-coated membrane (Promega, USA), while in case where the reactant uses the histone as the substrate, it was spotted on p81 cellulose paper. The both cases showed the same results in measurement of enzyme reaction activity. It was washed in 10 mM Tris-HCl (pH 8.0) and a 100 mM of NaCl solution five times, radioactivity generated from the phosphorylated peptide attached to the membrane was measured by a BAS radioactivity imaging measurement unit (Kodak), an enzyme reaction degree was quantitatively measured to measure the tyrosine kinase activity of DDR2 protein.

In order to measure self-phosphorylation activity of a DDR2 kinase activity portion, it was reacted in a reaction solution excluding the peptide

substrate in the above conditions, and the reactant underwent electrophoresis in 10% PAGE gel and then was stained using Kumagi dye to check existence of DDR2 kinase activity portion protein. Thereafter, the gel was dried and autoradiography was performed by using X-ray film to measure the self-phosphorylation degree of the DDR2 protein portion.

In order to measure inhibiting activity of the compounds, compounds dissolved in DMSO were previously added at various densities in an enzyme reaction solution, to which DDR2 kinase enzyme was added to proceed with an enzyme reaction to measure an inhibiting degree of enzyme activity at a specific density of each compound. Table 11 shows a density of each compound inhibiting 50% enzyme activity obtained by IC_{50} (density value of causing 50% activity inhibition) of each compound.

[Table 11]

compond	IC_{50} (uM)	compond	IC_{50} (uM)	compond	IC_{50} (uM)	compond	IC_{50} (uM)	compond	IC_{50} (uM)	compond	IC_{50} (uM)
VIa	<100	VIIe	<500	16	<100	42	<100	68	<500	94	<100
VIb	<100	VIIf	<500	17	<100	43	<100	69	<500	95	<500
VIc	<100	VIIg	<500	18	<500	44	<100	70	<500	96	<100
VId	<100	VIIh	<500	19	<500	45	<100	71	<500	97	<100
VIe	<100	VIIi	<500	20	<100	46	<500	72	<500	98	<100
Vif	<100	VIIj	<500	21	<500	47	<100	73	<100	99	<500
VIg	<100	VIIk	<500	22	<100	48	<100	74	<100	100	<500
VIh	<100	VIIl	<500	23	<100	49	<100	75	<500	101	<500
VIi	<100	VIIm	<500	24	<500	50	<100	76	<500	102	<500
VIj	<100	VIIo	<500	25	<500	51	<500	77	<500	103	<500
VIk	<100	VIIr	<500	26	<500	52	<100	78	<500	104	<100
VIl	<100	VIIs	<500	27	<500	53	<100	79	<100	105	<100
VIm	<100	VIIu	<500	28	<100	54	<100	80	<500	106	<100
VIn	<100	VIIv	<500	29	<100	55	<100	81	<500	107	<500
VIx	<100	VIIw	<500	30	<100	56	<500	82	<100	108	<500
VIq	<100	5	<500	31	<500	57	<100	83	<100	109	<500
VIr	<100	6	<500	32	<500	58	<100	84	<100	110	<500
VIs	<100	7	<500	33	<500	59	<100	85	<100	111	<100
VIt	<100	8	<100	34	<500	60	<100	86	<100	112	<500

As shown in Table 11, the compounds of the present invention can effectively inhibit the tyrosine kinase activity of DDR2 protein. Thus, the present invention is expected to have a remedial treatment effect with respect to hepatocirrhosis, rheumatism and metastatic cancers caused by the tyrosine kinase activity of DDR2 protein.

In the below experimentation, the compound 100 in Table 6 was used as a representative compound of the compounds of the present invention, but as noted in Table 11, the effect of the representative compound can be applied to the other compounds of the present invention.

In the experimentation for confirming the DDR2 tyrosine kinase inhibition mechanism of the compounds of the present invention, a reaction speed was obtained according to the enzyme activity measurement method while changing the amount of ATP. More specifically, the substrate of each density of 0, 0.2 uM and 1.2 uM of the representative compound 100 (Table 6) and then reciprocally plotted (Lubert Stryer, 4th revised version of biochemistry, Seoul foreign books, pp.202-205) which are generally known to check a change in a Y segment and x segment according to each density of the compounds. As shown in Figure 1, it is confirmed that when there is no change in the Y segment according to the density of the compound, the reaction speed V max does not change, and the changed in x segment indicating a Km value means that the DDR2 kinase activity inhibiting compounds of the present invention inhibit the DDR2 kinase activity by the ATP competitive mechanism.

Example 15: Measurement of Tyrosine Phosphorylation Inhibiting Activity of DDR2 Protein in HSC T6 Cell of Compounds of the Present Invention

Two hundred thousand HSC T6 cells (Prof. Fridman, Medical college of Mount Sini, N.Y. USA) were plated in each well of a 6-well cultivation dish, cultivated for 24 hours and processed at a 10 ug/ml density for 24 hours, or the compound (100 of Table 6) of the present invention dissolved in DMSO at a collagen 10 ug/ml density was processed according to each density (0, 5, 10 and 20 uM) for 24 hours, the cell was retrieved with a 1x lameli solution and fractured, and the cell fractured solution underwent the electrophoresis in 7% PAGE gel. The developed protein of the gel was moved to a nitrocellulose paper, and western-blotted to an antibody which specially recognizes human DDR2. It was confirmed that its amount is not much different from that of DDR2 protein at a position of130,000 dalton molecular mass, and its position was checked. The membrane was stripped, Western-blotted by using an antibody which specifically recognizes phosphorylated tyrosine, and it was verified that the tyrosine phosphorylation degree at a portion where the DDR2 is positioned is reduced according to a processing density of the representative compound 100 as shown in Figure 2.

With reference to Figure 2, It was confirmed that, like other studies reported by other researches, tyrosine phosphorlation of DDR2 was induced in the HSC T6 cell by the collagen treatment. The tyrosine phosphorylation of DDR2 indicates the activity of DDR2 kinase. However, as shown in Figure 2, it was also confirmed that the tyrosine phosphorylation of the DDR2 protein according to the collagen was reduced by the treatment with the representative compound 100. Accordingly, it was confirmed that the compound of the present invention has the activity of inhibiting activation of DDR2 protein by collagen.

Example 16: Measurement of cell growth inhibition activity of the compounds of the present invention

In order to measure the cell growth inhibition function of the compounds of the present invention, activity of a liver stellate cell HSC-T6, HT1080 and Rat2 cell was measured and compared. The cells were placed in the 96-well cultivation dish; 100 cells were placed in each well. After 24 hours elapses after the placement, in order to quantitatively measure the number of cells of day 0, three wells were fixed with formalin and, the compound (100 of Table 6) of the present invention as dissolved in DMSO was processed at a different density in the other remaining wells and then fixed in a formalin solution after 48 hours (day 2). Sulforodamine B was treated and dyed. The dye was then extracted with 0.1 M tris-HCl (pH 8.0) and its absorbancy was measured at A520 to quantitatively measure the number of cells. The absorbancy relatively indicates the number of living cells existing in the wells.

Absorbancy of the well of day 0 was set as 0%, absorbancy of the well left without the treamente of the compound for two days was set as 100%, and an absorbancy of 0 because there is no living cell in the well was set as -100%, and absorbancy at each density of each compound was calculated proportionally to indicate % of cell viability of respective compound-treated wells. Each experiment was performed with n=3 and a measurement value was indicated by obtaining an average value. The cell was cultivated in 5% carbon dioxide and at a below 37°C, the HSC-T6 cell was cultivated in DMEM+10% FBS, and the remaining cells were cultivated in RPMI1640+10% FBS.

Figure 3 shows the results of the experimentation. As shown in Figure 2, the compounds of the present invention exhibit relatively high growth inhibiting

activity over hepatic stellate cell HSC-T6 (-•-) compared with other cells. Thus, it is confirmed that the compounds of the present invention exhibit the specific growth-inhibiting activity with the liver stellate cell.

Example 17: Conformation of inducing apoptosis of the hepatic stellate cell of the compounds of the present invention

The compound (100 of Table 6) of the present invention dissolved in DMSO treated according to each density for the HSC T6 cell, and after 24 hours, an entire genome DNA was extracted according to a general method. The apoptosis was confirmed by measuring the degree of segmentation of DNA. The extracted DNA was developed in a 1.2% agarose gel, dyed with EtBr, and the segmented DNA was observed under UV. Figure 5 shows the results. As shown in Figure 5, many segmented DNAs are observed at a high processing density of the compounds of the present invention. Therefore, it is confirmed that the compounds of the present invention induces apoptosis of the HSC T6 cell.

Example 18: Confirmation of anti-fibrosis effect of the compounds of the present invention over liver cirrhosis

A bile duct of a whistar rat aged 7 weeks was sutured to induce a liver cirrhosis. The compound (100 of Table 6) dissolved in DMSO at a density of 10mg/kg was injected to its tail vein every day for two weeks. As a reference group, a rat to which only DMSO (carrier) was injected after suturing the bile duct was used, and as a normal reference group, a rat which got a placebo operation without suturing its bile duct was used. As for collagen quantitative measurement of the liver tissue, an amount of hydroxy furorin in the liver tissue was

quantitatively measured using a general method. Table 12 shows the results.

[Table 12]

Experimentation	amount of hydroxy furorin (mg/g liver tissue)
Placebo group	1.96±0.21
Bile duct suture + carrier	4.93±0.41
Bile duct suture + compound 100	2.23±0.17

As noted in Table 12, the case where the bile duct was sutured, liver cirrhosis was caused according to an increase in the number of hydroxy prolin, compared to the case where the bile duct was not sutured. In the case where the liver cirrhosis was caused, the case where the compound was processed shows that the increase of the hydroxy prolin is mitigated. Accordingly, it is considered that the compounds of the present invetinon have the anti-fibrous activity over the liver cirrhosis.

According to a different method in which when a liver tissue of a rat that has the liver cirrhosis because of the sutured bile duct was processed by the compound of the present invention, collagen deposit was reduced, The liver tissue was freezed, a thin fragment was created and dyed by using a Masson Stain Method for generally dyeing collagen deposit of a tissue, and then observed with an optical microscope of 400 times magnification . Figure 6 shows the results. A portion dyed in a blue color shows where the deposited collagen was dyed, while a portion dyed in a red color is cells of the liver tissue.

Example 19: Measurement of synovial fibroblase growth inhibiting activity

of the compound of the present invention

Synovial fibroblasts extracted from a rheumatism patient which has been cultivated from an animal cell cultivator at 37°C in a DMEM medium including 10% FBS while supplying 5% carbon dioxide were seeded in 24-well cultivation dish, 5000 synovial fibroblase per well, and cultivated for one more day. Formalin with the same volume as the medium was added in three wells, fixed 30 minutes, washed with water, and then dried, while the other remaining wells were processed with the compound (100 of Table 6) of the present invention with n=3 according to each density for 48 hours to cultivate it, or they were continuously cultivated for 48 hours without being processed with the compound, formalin with the same volume as the medium was added to each well, fixed 30 minutes, washed with water, and then, dried. The formalin-fixed cell was dyed in a sulferodamine B solution using a general method and the sulferodamine adsorbed in the cell was removed with 0.1 M Tris-HCl (pH 8.0), and its absorbancy was measured at the wavelength of 520 nM, to quantitatively measure the number of relative cells in each well. By determining the number of cells (namely, absorbancy) in wells prior to treating the compound as a reference point (0%), the number of cells (namely, absorbancy) in wells continuously cultivated for 48 yours without treating the compound as 100%, and the case where cells in wells were completely destructed (absorbancy 0) as -100%, the number of cells (namely, absorbancy) when the compound of the present invention was treated according to each density for 48 hours were calculated according to a proportional expression to obtain a % cell viability at each compound density, which is as shown in Figure 7.

Figure 7 shows that the compounds of the present invention have the

inhibiting activity over growth of synovial fibroblase, and it is noted that the growth inhibiting activity increases in proportion to the density of the treated compound. Thus, it is considered that the compound of the present invention can have the remedial effect over the rheumatism caused by the abnormal growth of the synovial fibroblasts.

Example 20: Measurement of effect on the MMP-1 mRNA of the compounds of the present invention

Synovial fibroblasts taken from a rheumatism patient was cultivated in a dish with a diameter of 10cm with a DMEM medium including 10 % FBS under the condition of 5% CO_2. When the cells were actively growing with a cell density of 50% in the cultivation dish, the compound of the present invention dissolved in the DMSO was treated at the density of 10 uM for 24 hours, or as a reference group, the compound was not treated and left as it is 24 hours, and then, the entire RNA of the cells in the cultivation dish were purified. For purification, Triazol Reagent (catalog No. 15596-026) purchased from GIBCO BRL Co. was used, and as the purification method, an 'instruction for RNA Isolation' method furovided when the GIBCO BRL Co. sells Triazol Reagent was taken for sepration. The 10 ug of the entire purified RNA underwent electrophoresis in a formaldehyde-agarose gel, and mRNA was moved to a nitran membrane. An MMP-1 probe marked with ^{32}P radioactive isotope was prepared by using a kit purchased from Beringer-Ingelheim by using an MMP-1 c-DNA fragmentation. The amount of mRNA of the MMP-1 was quantitatively measured through common northern blotting by using the prepared probe. Figure 8 shows the results.

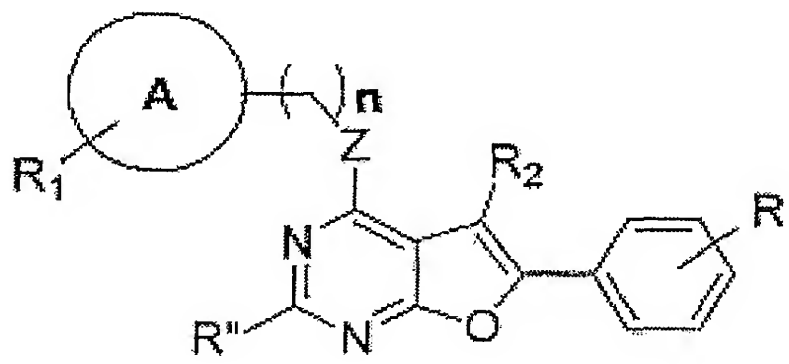
As shown in Figure 8, when the case that the compound of the present invention was treated (10 uM) and when the compound of the present invention was not treated (0 uM) are compared, it can be shown that the compound of the present invention has the effect of reducing the amount of mRNA of the MMP-1. Thus, it can be considered that the compound of the present invention has the remedial activity over the rheumatism caused by the incrase of the amount of MMP-1.

As so far described, the new furopyrimidine compounds of the present invention have the excellent inhibiting activity over the tyrosine kinase activity of DDR2 protein, and thus it can be applied as a remedial agent of various illnesses caused by the tyrosine kinase activity of DDR2. Especially, the compounds of the present invention can be advantageously used as a remedy for hepatocirrhosis, rheumatoid or cancer.

What is claimed is:

1. A furopyrimidine compound represented by chemical formula 1, its precursor or its pharmaceutically acceptable salt:

[Chemical formula 1]



wherein, Z is O, S or NH,

n represents an integer between 0 and 4,

R_1 is single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, amidine, C1-C4 alkyl group, C1-C4 halo alkyl group, C1-C7 alkoxy group, C1-C4 alkyl amino group, C1-C4 alkylthio group, C1-C4 alkyl amide group, C1-C4 acyl amino group, C1-C4 acyl oxy group, C1-C4 alkyl sulfone amide group, C1-C4 alkyl sulfonate group, imidic acid C1-C4 alkyl ester, thioimidic acid C1-C4 alkyl ester, hydroxy or amino, morpholine, acetate, acetamide, methanesulfoneamide group-substituted methyl group, C1-C4 halo alkyl group, C1-C4 alkoxy group, or a halogen-substituted benzyl oxy group,

R" represents hydrogen, C1-C4 alkyl group, C1-C4 halo alkyl group, C1-C7 alkoxy group, C1-C4 alkyl amino group, C1-C4 alkyl thio group, C1-C4 alkyl amide group, C1-C4 acyl amino group, C1-C4 acyl oxy group, imidic acid C1-C4 alkyl ester, thiol-imidic acid C1-C4 alkyl ester, hydroxy or amino, morpholine, acetate, acetamide, methanesulfoneamide group-substituted methyl group, C1-

C4 halo alkyl group, C1-C4 alkoxy group, or a halogen-substituted phenyl group,

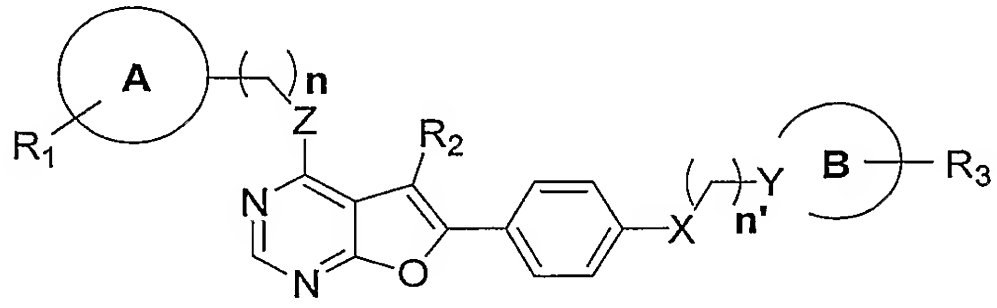
A ring indicates benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyrazine, pyridazine, pyrimidine, cyclo hexyl, piperidine or morpholine,

R_2 indicates hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C5 alkyl group, C1-C5 haloalkyl group, alkylester, phenyl group, halogen-substituted phenyl group, C1-C4 alkoxy group-substituted phenyl group or C1-C4 haloalkoxy group-substituted phenyl group, and

R is single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, amidine, C1-C4 alkyl group, C1-C4 haloalkyl group, C1-C7 alkoxy group, C1-C4 alkylamino group, C1-C4 alkylthio group, C1-C4 alkylamide group, C1-C4 acylamino group, C1-C4 acyloxy group, or C1-C4 alkylsufoneamide group.

2. A furopyrimidine compound represented by chemical formula 2, its precursor or its pharmaceutically acceptable salt:

[Chemical formula 2]



wherein, Z is O, S or NH,

X is O, S or NH,

Y is C or N,

n is an integer between 0 and 4,

n' is an integer between 0 and 4,

R_1 and R_3 are independently identical or different and single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, amidine, C1-C4 alkyl group, C1-C4 halo alkyl group, C1-C7 alkoxy group, C1-C4 alkyl amino group, C1-C4 alkylthio group, C1-C4 alkyl amide group, C1-C4 acyl amino group, C1-C4 acyl oxy group, C1-C4 alkyl sulfoneamide group, C1-C4 alkyl sulfonate group, imidic acid C1-C4 alkyl ester, thioimidic acid C1-C4 alkyl ester, hydroxy or amino, morpholine, acetate, acetamide, methanesulfoneamide group-substituted methyl group, C1-C4 halo alkyl group, C1-C4 alkoxy group, or a halogen-substituted benzyl oxy group,

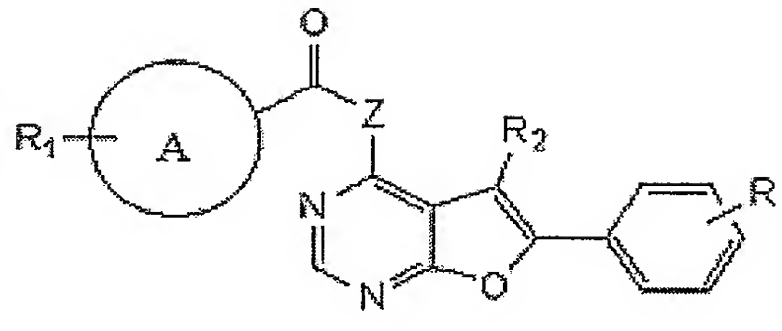
A ring indicates benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, cyclo hexyl, piperidine or morpholine,

B ring indicates pyrrole, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, piperidine, pyrolidine, piperazine, morpholine, thiomorpholine, imidazoline, pyrolidon, C3-C6 cycloalkyl or piperidon, and

R_2 indicates hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C5 alkyl group, C1-C5 haloalkyl group, alkylester, phenyl group, halogen-substituted phenyl group, C1-C4 alkoxy group-substituted phenyl group or C1-C4 haloalkoxy group-substituted phenyl group.

3. A furopyrimidine compound represented by chemical formula 3, its precursor and its pharmaceutically acceptable salt:

[Chemical formula 3]



wherein, Z is O, S or NH,

n is an integer between 0 and 4,

R_1 is single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, amidine, C1-C4 alkyl group, C1-C4 halo alkyl group, C1-C7 alkoxy group, C1-C4 alkyl amino group, C1-C4 alkylthio group, C1-C4 alkyl amide group, C1-C4 acyl amino group, C1-C4 acyl oxy group, C1-C4 alkyl sulfone amide group, C1-C4 alkyl sulfonate group, imidic acid C1-C4 alkyl ester, thioimidic acid C1-C4 alkyl ester, hydroxy or amino, morpholine, acetate, acetamide, methanesulfoneamide group-substituted methyl group, C1-C4 halo alkyl group, C1-C4 alkoxy group, or a halogen-substituted benzyl oxy group,

A ring indicates benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, cyclo hexyl, piperidine or morpholine,

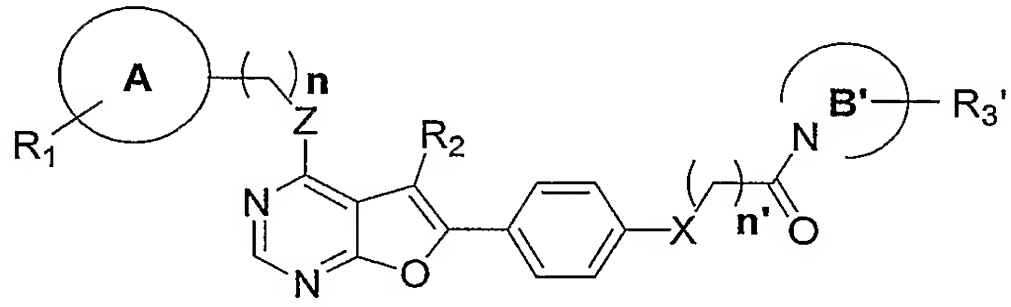
R_2 indicates hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C5 alkyl group, C1-C5 haloalkyl group, alkylester, phenyl group, halogen-substituted phenyl group, alkoxy group-substituted phenyl group, or C1-C4 haloalkoxy group-substituted phenyl group, and

R is single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C4 alkyl group, amidine, C1-C4 haloalkyl group, C1-C7 alkoxy group, C1-C4 alkylamino group,

C1-C4 alkyl thio group, C1-C4 alkyl amide group, C1-C4 acylamino group, C1-C4 acyloxy group, or C1-C4 alkylsufoneamide group.

4. A furopyrimidine compound represented by chemical formula 4, its precursor or its pharmaceutically acceptable salt:

[Chemical formula 4]



wherein, Z is O, S or NH,

X indicates O, S or NH,

n is an integer between 0 and 4,

n' is an integer between 0 and 4,

R_1 and R_3' are independently identical or different, and single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, amidine, C1-C4 alkyl group, C1-C4 halo alkyl group, C1-C7 alkoxy group, C1-C4 alkyl amino group, C1-C4 alkylthio group, C1-C4 alkyl amide group, C1-C4 acyl amino group, C1-C4 acyl oxy group, C1-C4 alkyl sulfoneamide group, C1-C4 alkyl sulfonate group, imidic acid C1-C4 alkyl ester, thioimidic acid C1-C4 alkyl ester, hydroxy or amino, morpholine, acetate, acetamide, methanesulfoneamide group-substituted methyl group, C1-C4 halo alkyl group, C1-C4 alkoxy group, or a halogen-substituted benzyl oxy group, A ring indicates benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, cyclo hexyl,

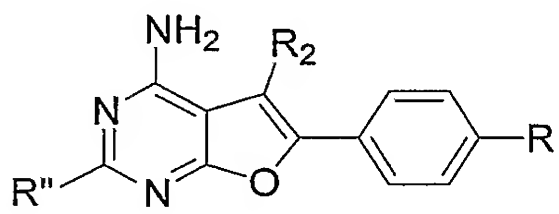
piperidine or morpholine,

B' ring indicates pyrrole, pyrazine, pyridazine, pyrimidine, piperidine, pyrolidine, piperazine, morpholine, thiomorpholine, imidazoline, pyrolidon or piperidon, and

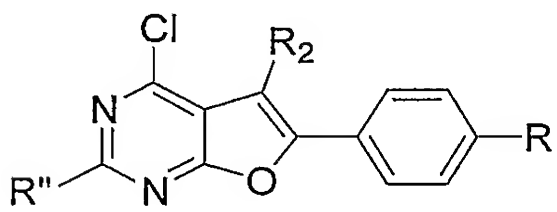
R_2 indicates hydrogen, halogen, cyano, nitro, hydroxyl, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C5 alkyl group, C1-C5 haloalkyl group, alkylester, phenyl group, halogen-substituted phenyl group, C1-C4 alkoxy group-substituted phenyl group, or C1-C4 haloalkoxy group-substituted phenyl group.

5. A furopyrimidine compound represented by chemical formula XI or XII, its precursor or its pharmaceutically acceptable salt.

[Chemical formula XI]



[Chemical formula XII]



wherein, R_2 indicates hydrogen, halogen, cyano, nitro, hydroxyl, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C5 alkyl group, C1-C5 haloalkyl group, alkylester, phenyl group, halogen-substituted phenyl group, C1-C4 alkoxy group-substituted phenyl group, or C1-C4 haloalkoxy group-substituted phenyl group,

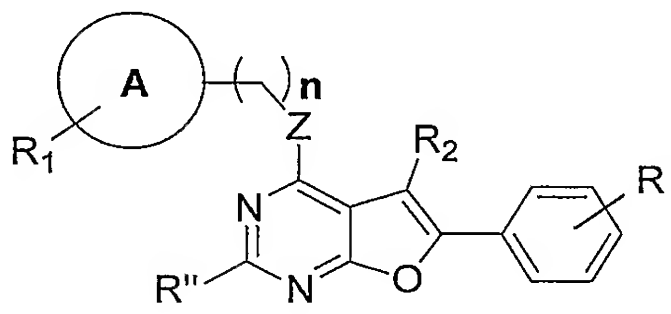
R is single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C4 alkyl group,

amidine, C1-C4 haloalkyl group, C1-C7 alkoxy group, C1-C4 alkylamino group, C1-C4 alkyl thio group, C1-C4 alkyl amide group, C1-C4 acylamino group, C1-C4 acyloxy group, or C1-C4 alkylsufoneamide group, and

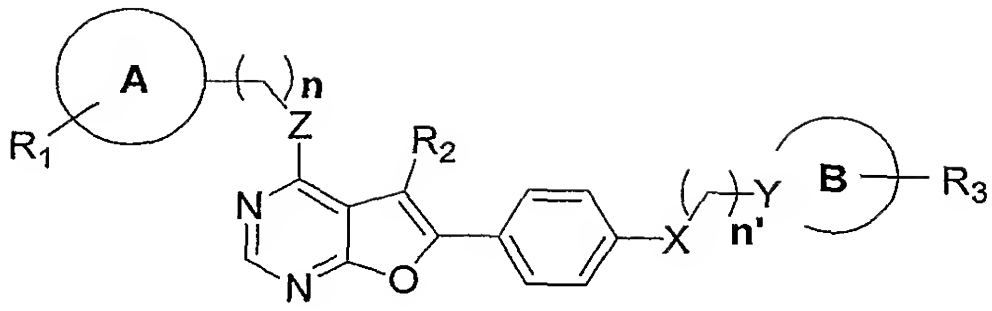
R" represents hydrogen, C1-C4 alkyl group, C1-C4 halo alkyl group, C1-C7 alkoxy group, C1-C4 alkyl amino group, C1-C4 alkyl thio group, C1-C4 alkyl amide group, C1-C4 acyl amino group, C1-C4 acyl oxy group, imidic acid C1-C4 alkyl ester, thiol-imidic acid C1-C4 alkyl ester, hydroxy or amino, morpholine, acetate, acetamide, methanesulfoneamide group-substituted methyl group, C1-C4 halo alkyl group, C1-C4 alkoxy group, or a halogen-substituted phenyl group.

6. A tyrosine kinase activity inhibitor of DDR2 protein, comprising as an effective ingredient a therapeutically effective amount of one or more selected from the group consisting of furopyrimidine derivatives represented by Chemical formula 1, Chemical formula 2, Chemical formula 3, Chemical formula 4, Chemical formula XI and Chemical formula XII, and its pharmacologically acceptable salt:

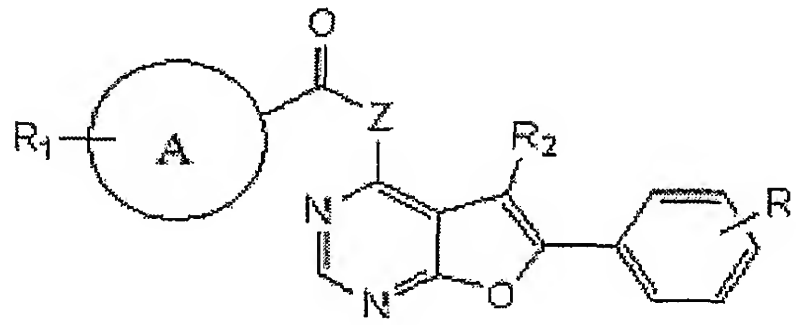
[Chemical formula 1]



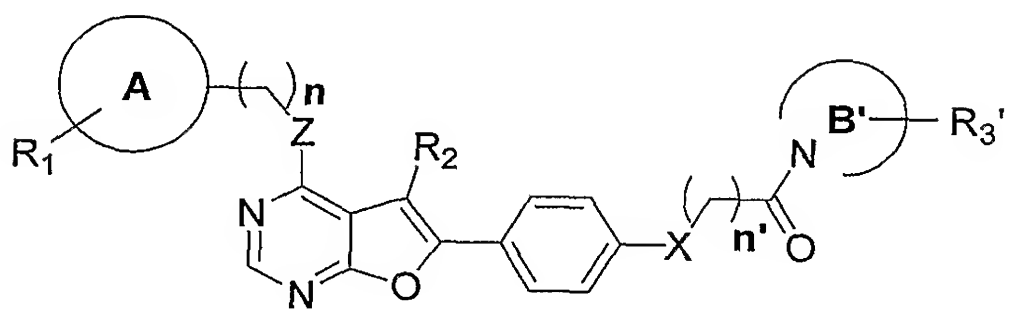
[Chemical formula 2]



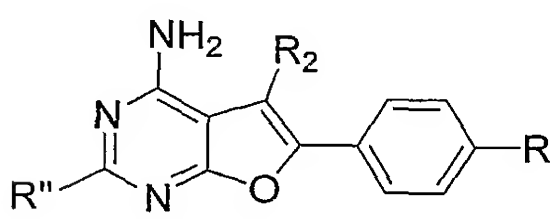
[Chemical formula 3]



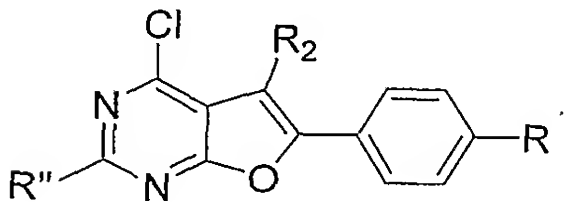
[Chemical formula 4]



[Chemical formula XI]



[Chemical formula XII]



wherein, Z is O, S or NH,

Y is C or N,

X is O, S or NH,

n is an integer between 0 and 4,

n' is an integer between 0 and 4,

R_1, R_3 and R_3' are independently identical or different and single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, amidine, C1-C4 alkyl group, C1-C4 halo alkyl group, C1-C7 alkoxy group, C1-C4 alkyl amino group, C1-C4 alkylthio group, C1-C4 alkyl amide group, C1-C4 acyl amino group, C1-C4 acyl oxy group, C1-C4 alkyl sulfoneamide group, C1-C4 alkyl sulfonate group, imidic acid C1-C4 alkyl ester, thioimidic acid C1-C4 alkyl ester, hydroxy or amino, morpholine, acetate, acetamide, methanesulfoneamide group-substituted methyl group, C1-C4 halo alkyl group, C1-C4 alkoxy group, or a halogen-substituted benzyl oxy group,

A ring indicates benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, cyclo hexyl, piperidine or morpholine,

B ring or B' ring indicates pyrrole, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, piperidine, pyrolidine, piperazine, morpholine, thiomorpholine, imidazoline, pyrolidon, C3-C6 cycloalkyl or piperidon,

R_2 indicates hydrogen, halogen, cyano, nitro, hydroxyl, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C5 alkyl group, C1-C5 haloalkyl group, alkylester, phenyl group, halogen-substituted phenyl group, C1-C4 alkoxy group-substituted phenyl group, or C1-C4 haloalkoxy group-substituted phenyl group,

R is single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C4 alkyl group,

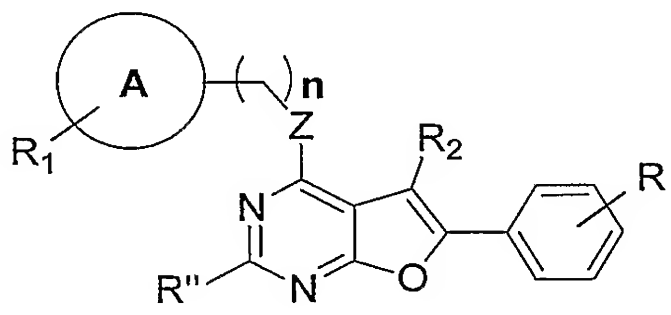
amidine, C1-C4 haloalkyl group, C1-C7 alkoxy group, C1-C4 alkylamino group, C1-C4 alkyl thio group, C1-C4 alkyl amide group, C1-C4 acylamino group, C1-C4 acyloxy group, or C1-C4 alkylsufoneamide group, and

R" represents hydrogen, C1-C4 alkyl group, C1-C4 halo alkyl group, C1-C7 alkoxy group, C1-C4 alkyl amino group, C1-C4 alkyl thio group, C1-C4 alkyl amide group, C1-C4 acyl amino group, C1-C4 acyl oxy group, imidic acid C1-C4 alkyl ester, thiol-imidic acid C1-C4 alkyl ester, hydroxy or amino, morpholine, acetate, acetamide, methanesulfoneamide group-substituted methyl group, C1-C4 halo alkyl group, C1-C4 alkoxy group, or a halogen-substituted phenyl group.

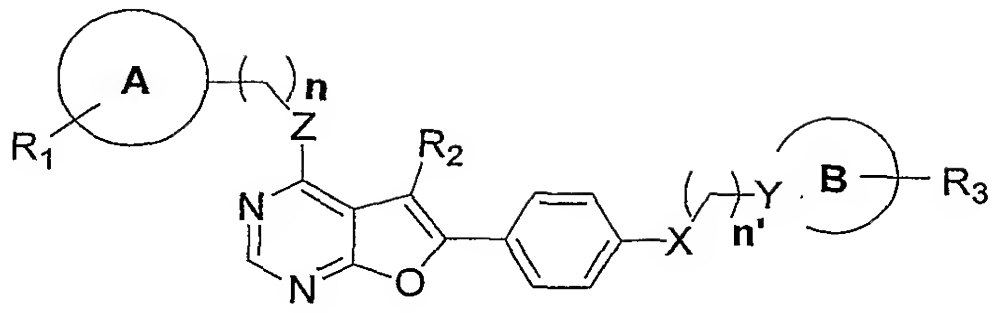
7. The tyrosine kinase activity inhibitor of DDR2 protein of claim 6 additionally contains pharmaceutically acceptable carrier or excipient.

8. A pharmaceutical composition for treating a desease caused by tyrosine kinase activity of DDR2 protein, comprising as an effective ingredient a therapeutically effective amount of one or more selected from the group consisting of furopyrimidine derivativea represented by Chemical formula 1, Chemical formula 2, Chemical formula 3, Chemical formula 4, Chemical formula VII and Chemical formula XI, and its pharmacologically acceptable salt.

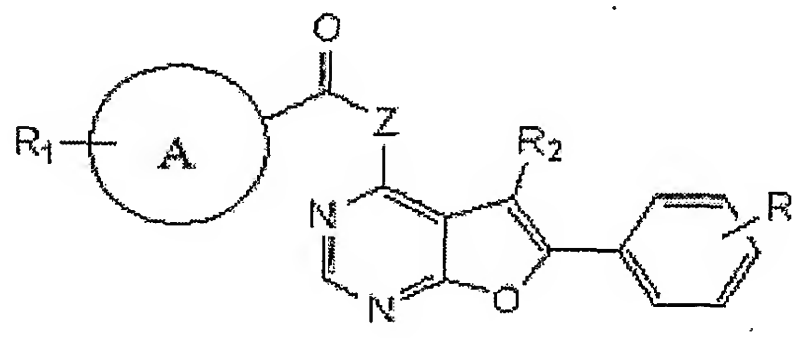
[Chemical formula 1]



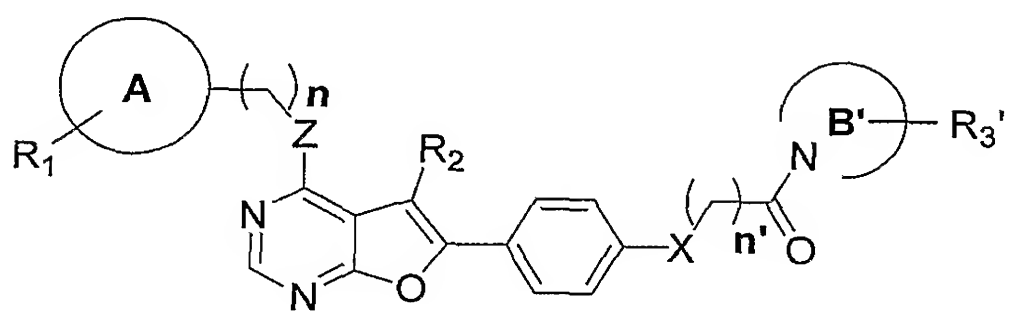
[Chemical formula 2]



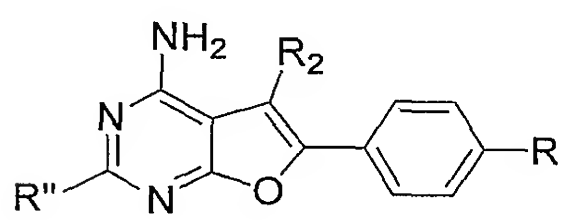
[Chemical formula 3]



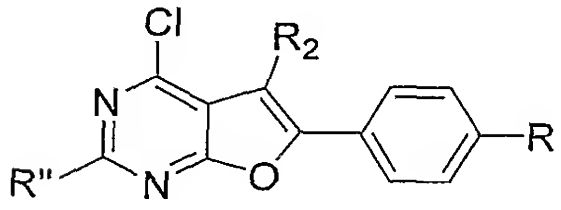
[Chemical formula 4]



[Chemical formula XI]



[Chemical formula XII]



wherein, Z is O, S or NH,

Y is C or N,

X is O, S or NH,

n is an integer between 0 and 4,

n' is an integer between 0 and 4,

R_1, R_3 and R_3' are independently identical or different and single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, amidine, C1-C4 alkyl group, C1-C4 halo alkyl group, C1-C7 alkoxy group, C1-C4 alkyl amino group, C1-C4 alkylthio group, C1-C4 alkyl amide group, C1-C4 acyl amino group, C1-C4 acyl oxy group, C1-C4 alkyl sulfoneamide group, C1-C4 alkyl sulfonate group, imidic acid C1-C4 alkyl ester, thioimidic acid C1-C4 alkyl ester, hydroxy or amino, morpholine, acetate, acetamide, methanesulfoneamide group-substituted methyl group, C1-C4 halo alkyl group, C1-C4 alkoxy group, or a halogen-substituted benzyl oxy group,

A ring indicates benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, cyclo hexyl, piperidine or morpholine,

B ring or B' ring indicates pyrrole, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, piperidine, pyrolidine, piperazine, morpholine, thiomorpholine, imidazoline, pyrolidon, C3-C6 cycloalkyl or piperidon,

R_2 indicates hydrogen, halogen, cyano, nitro, hydroxyl, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C5 alkyl group, C1-C5 haloalkyl group, alkylester, phenyl group, halogen-substituted phenyl group, C1-C4 alkoxy group-substituted phenyl group, or C1-C4 haloalkoxy group-substituted phenyl group,

R is single-substituted or independently double-substituted by hydrogen, halogen, cyano, nitro, hydroxy, amino, CO_2H, $CONH_2$, $CSNH_2$, C1-C4 alkyl group,

amidine, C1-C4 haloalkyl group, C1-C7 alkoxy group, C1-C4 alkylamino group, C1-C4 alkyl thio group, C1-C4 alkyl amide group, C1-C4 acylamino group, C1-C4 acyloxy group, or C1-C4 alkylsufoneamide group, and

R" represents hydrogen, C1-C4 alkyl group, C1-C4 halo alkyl group, C1-C7 alkoxy group, C1-C4 alkyl amino group, C1-C4 alkyl thio group, C1-C4 alkyl amide group, C1-C4 acyl amino group, C1-C4 acyl oxy group, imidic acid C1-C4 alkyl ester, thiol-imidic acid C1-C4 alkyl ester, hydroxy or amino, morpholine, acetate, acetamide, methanesulfoneamide group-substituted methyl group, C1-C4 halo alkyl group, C1-C4 alkoxy group, or a halogen-substituted phenyl group.

9. The pharmaceutical composition of claim 8, wherein the desease caused by the DDR2 tyrosine kinase activity is hepatocirrhosis, rheumatism or cancer.

10. The pharmaceutical composition of claim 8, additionally contains pharmaceutically acceptable carrier or excipient.

FIG. 1

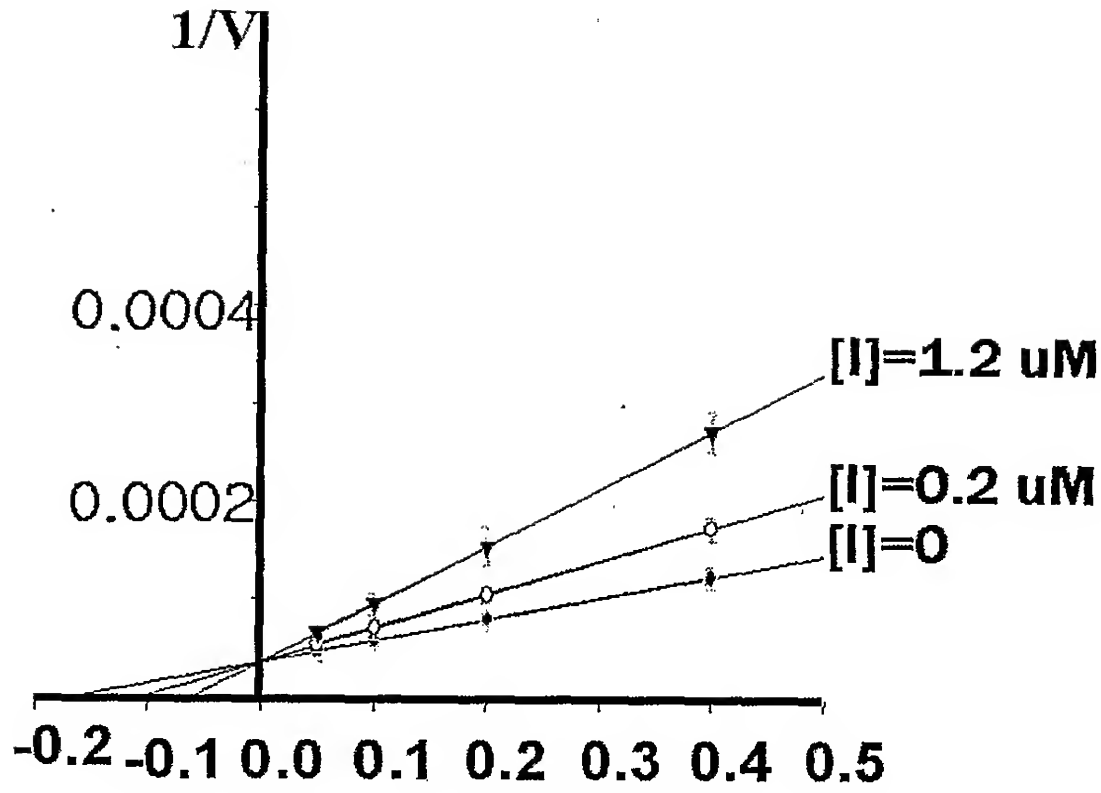

1/V
0.0004
0.0002
[I]=1.2 uM
[I]=0.2 uM
[I]=0
-0.2 -0.1 0.0 0.1 0.2 0.3 0.4 0.5
1/(ATP)

FIG. 2

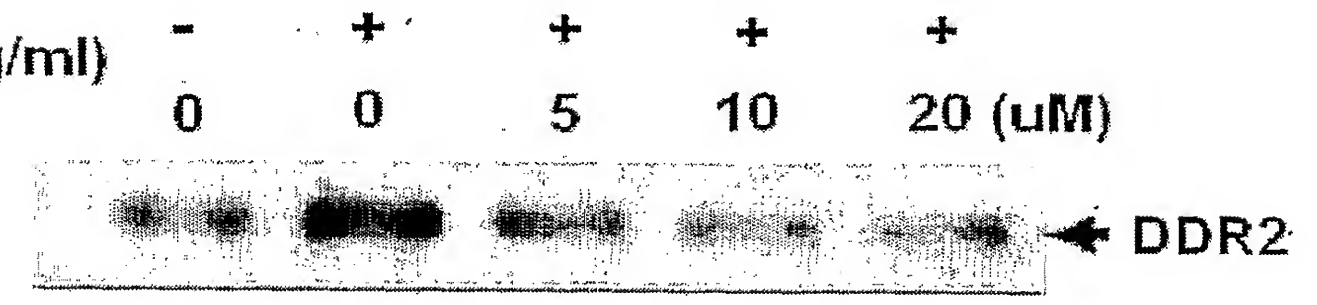

Collagen (10ug/ml) - + + + +
Compound #100 0 0 5 10 20 (uM)
DDR2

FIG. 3

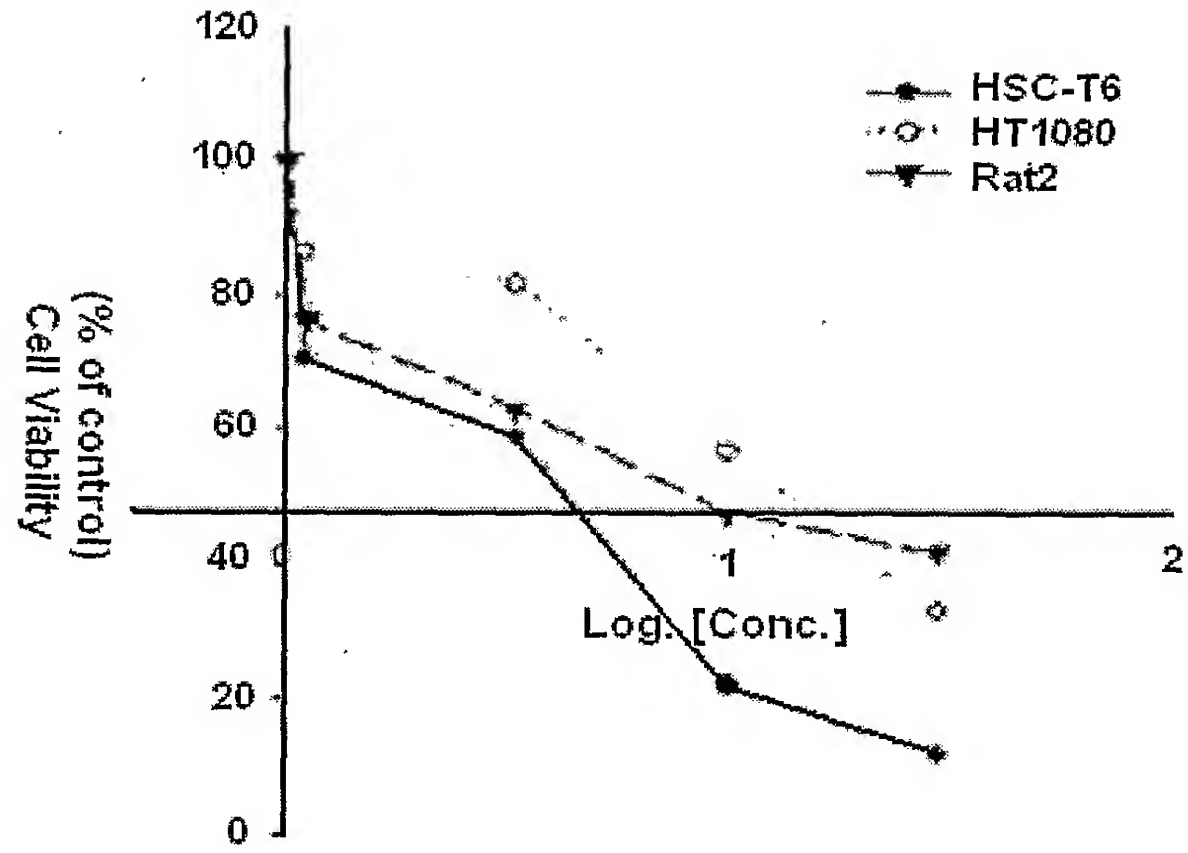
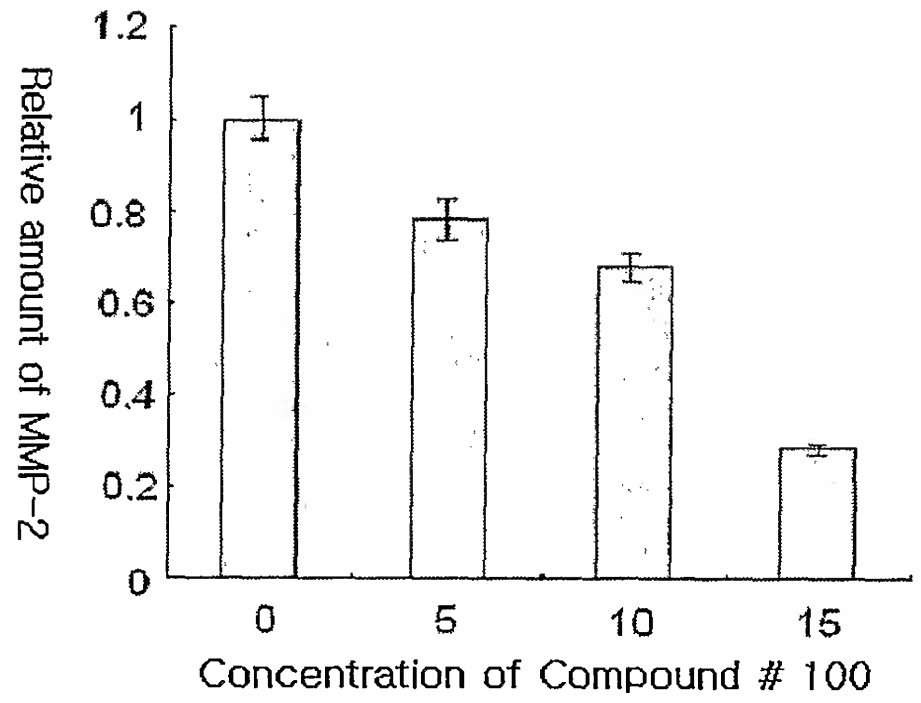
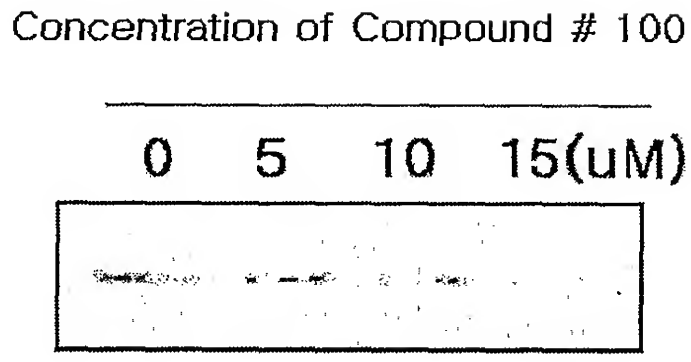

120
100
80
60
40
20
0
(% of control)
Cell Viability
HSC-T6
HT1080
Rat2
1
2
Log. [Conc.]

FIG. 4


1.2
1
0.8
0.6
0.4
0.2
0
Relative amount of MMP-2
0
5
10
15
Concentration of Compound # 100

(a)


Concentration of Compound # 100
0 5 10 15(uM)

(b)

FIG. 5

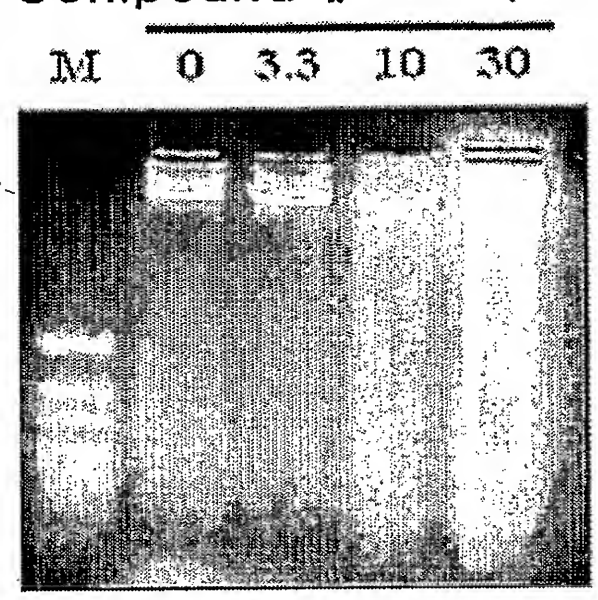

Compound # 100 (uM)
M 0 3.3 10 30

FIG. 6

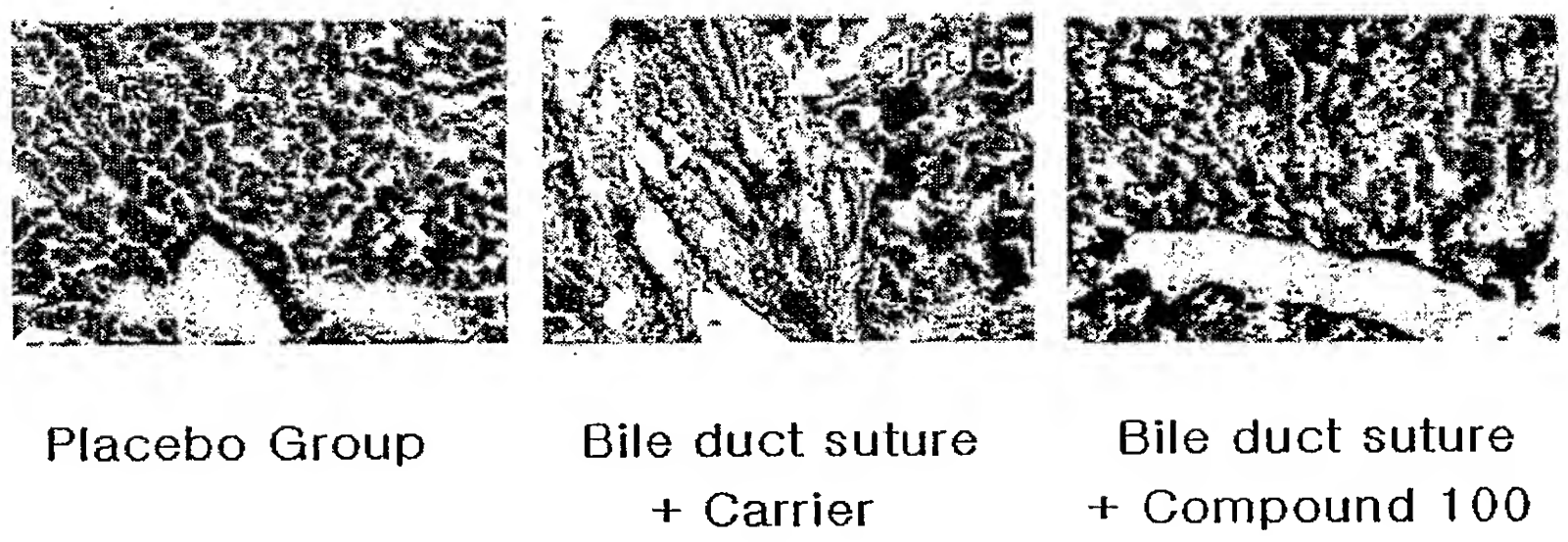

Placebo Group
Bile duct suture
+ Carrier
Bile duct suture
+ Compound 100

FIG. 7

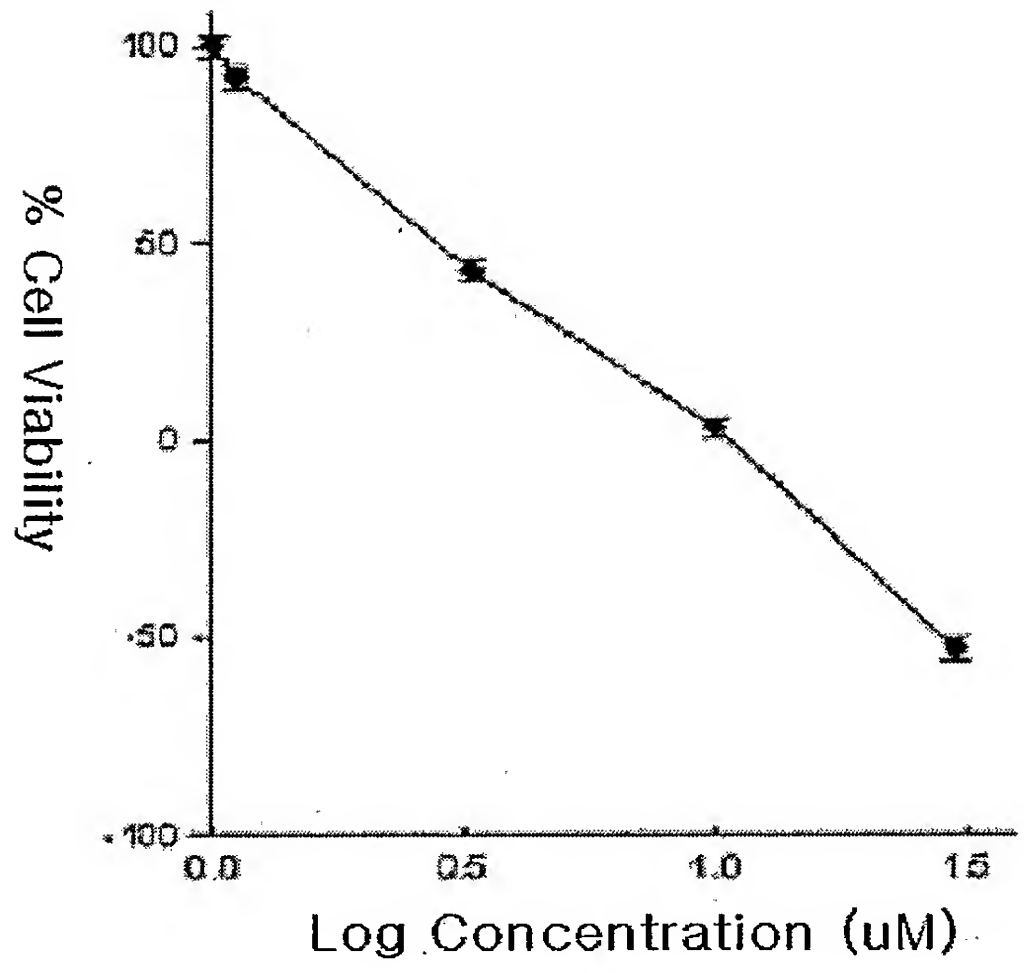
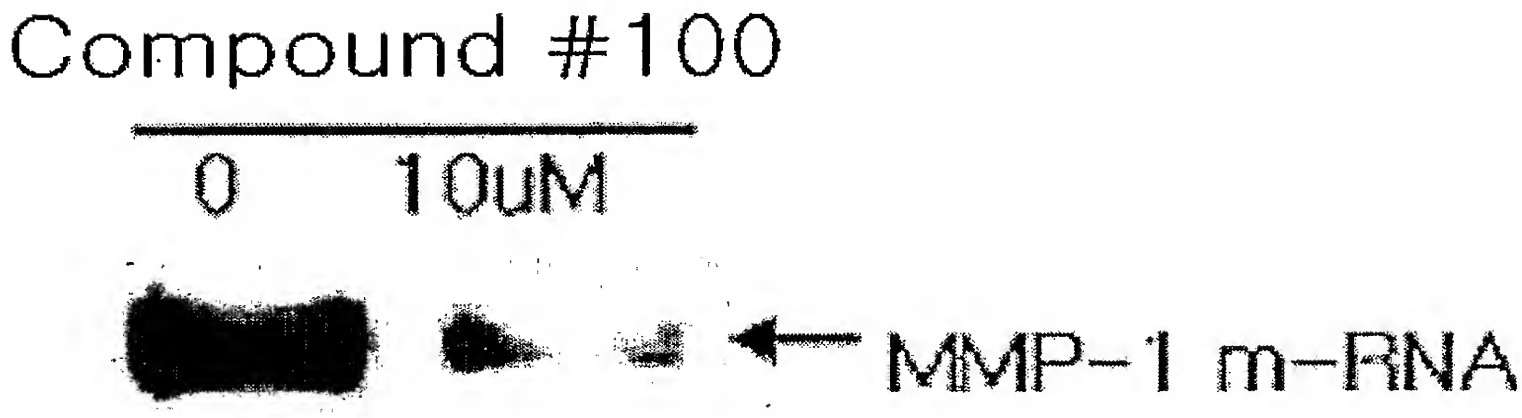

100
50
0
-50
-100
% Cell Viability
0.0
0.5
1.0
1.5
Log Concentration (uM)

FIG. 8


Compound #100
0
10uM
MMP-1 m-RNA

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2005/000019

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 491/048

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC7 C07D 491/048

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean Patents and applications for inventions since 1975.

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search terms used)

STN(CASLINK)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 03022852 A2 (GLAXOSMITHKLINE K.K.) 20 MARCH 2003, see entire document.	1 - 5 1 - 10
X Y	WO 03018589 A1 (BAYER AKTIENGESELLSCHAFT) 06 MARCH 2003, see entire document.	1 - 5 1 - 10
X Y	WO 02092603 A1 (NOVARTIS AG) 21 NOV. 2002, see entire document.	1 - 5 1 - 10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 APRIL 2005 (14.04.2005)	**14 APRIL 2005 (14.04.2005)**

Name and mailing address of the ISA/KR	Authorized officer
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Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2005/000019

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03022852 A2	20-03-2003	US 20050004142 A1	06-01-2005
		EP 1425284 A2	09-06-2004
WO 03018589 A1	06-03-2003	US 20040259888 A1	23-12-2004
		EP 1425283 B1	16-03-2005
WO 02092603 A1	21-11-2002	US 20040152892 A1	05-08-2004
		EP 1390371 A1	25-02-2004